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14. ABSTRACT

Our major objective is to develop an electronic application capable of integrating and semantically standardizing electronic medical record (EMR) data to generate de-identified datasets populated with longitudinal clinical data drawn from diverse sources. In Year 1 of our project, we have successfully built the infrastructure to support this project. In year 2, we used the EMR output and selected genetic information to construct predictive models of the outcomes of complex digestive diseases using Bayesian network (BN) analysis of the generated databases. We plan on comparing performance among models generated using EMR data alone and data from disease-specific clinical research repositories (with and without genetic data). In collaboration with Walter Reed Army Medical Center, we will share our data acquisition strategies and algorithmic model development. In year 3, we built predictive models at both Walter Reed and Pittsburgh to evaluate the feasibility of sharing data and models. The integration of the two distinct patient populations will lay the groundwork for future data-sharing projects of mutual interest.

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None provided

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Contents

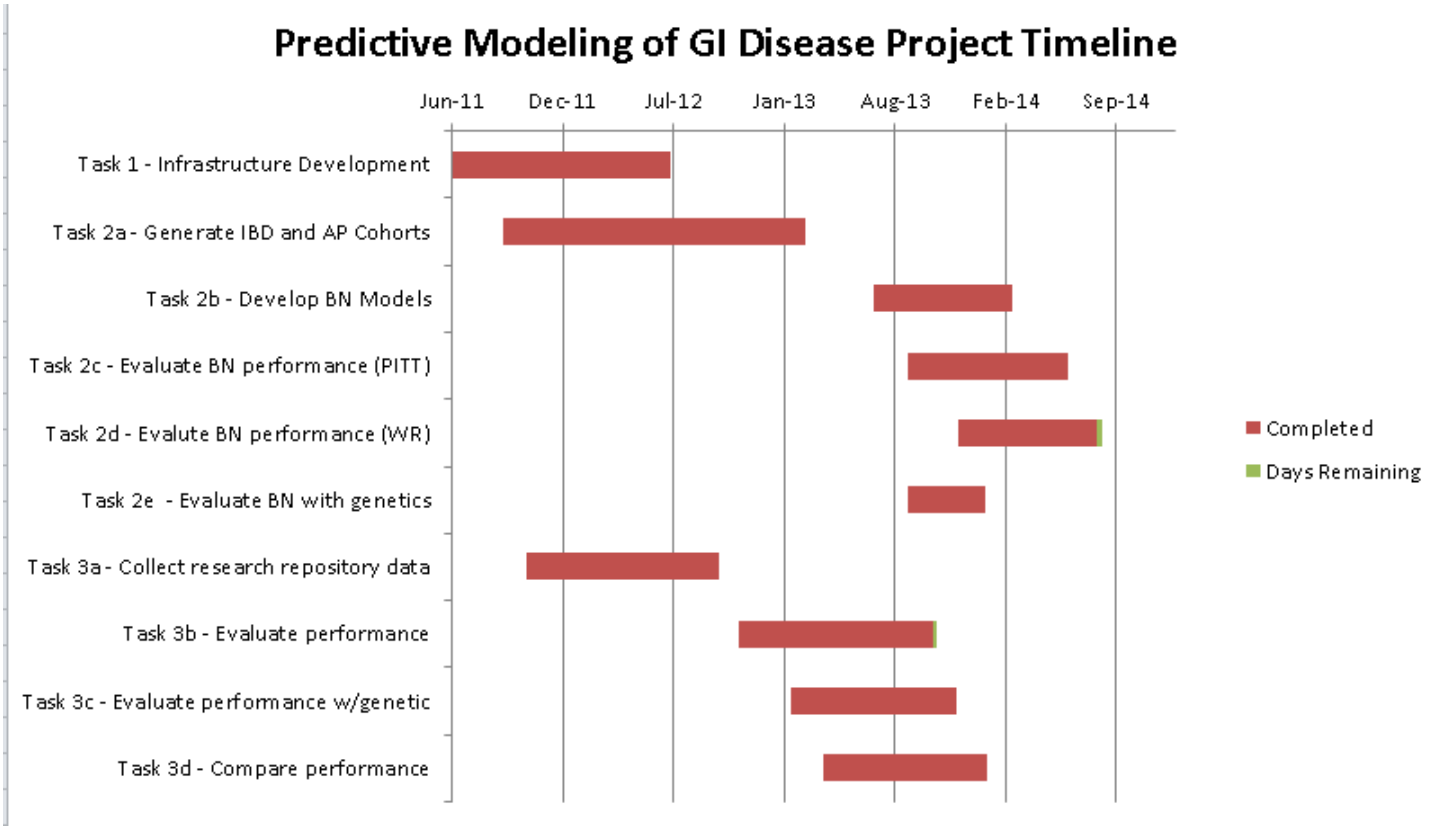
Introduction

Complex disorders result from the interaction of genetic, metabolic, and environmental factors that may not by themselves produce disease but can combine to alter disease severity and its progression. These factors, which may be contained in an electronic medical record (EMR) system, can be used to build predictive models of disease with the hope of improving disease management.

It is difficult to find these factors in EMR systems as the information is in both structured and unstructured formats that have been collected over many years. Research studies, in contrast, only collect a limited snapshot of a patient's clinical history. This information is usually not rich enough to develop predictive models. To construct a useful patient profile for analysis requires collecting disease progression and treatment information from a wide variety of sources that may span twenty years or more.

Our study goal is to develop the Megascope application to provide a software platform for the integration of clinical, genomic and research data collected from multiple sources. The University of Pittsburgh's Department of Biomedical Informatics (DBMI) and Division of Gastroenterology is an ideal collaboration to achieve this goal given our history of successful development of informatics applications and clinical research in complex GI diseases.

We will test the ability of Megascope to support predictive modeling of the outcomes of complex digestive diseases using Bayesian network (BN) analysis of the generated databases. We will further compare performance among models generated using EMR data alone and data from disease-specific clinical research repositories (with and without genetic data). Our timeline is presented below:



Body

Final report on Technical Objective 1 – Infrastructure Development

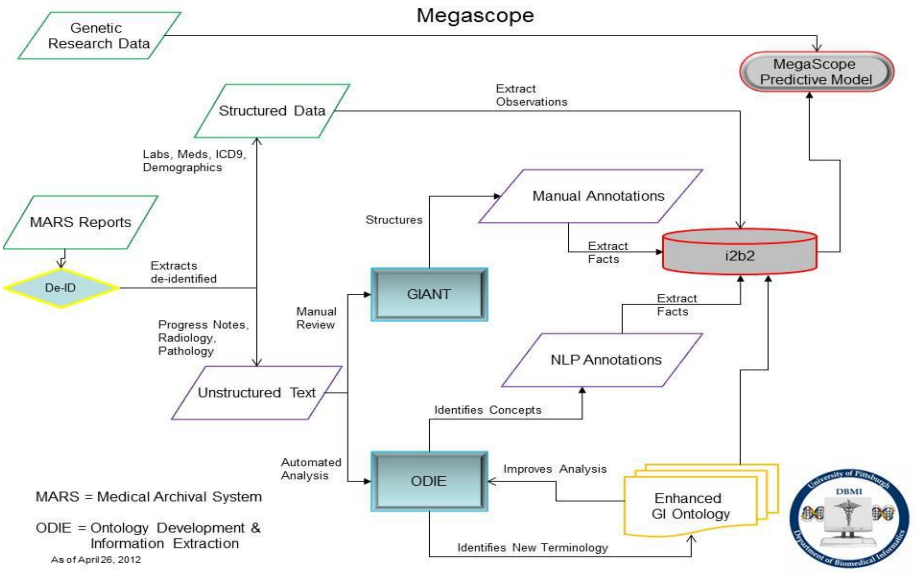
In our initial grant award year, we successfully built an application called Megascope to support our project goals. We realized early in the project that we needed to have a robust, open-source platform that would support the integration of clinical and genetic data. We also wanted to have an application that would not require a lengthy development cycle for creating data models. We decided to use the i2b2 (www.i2b2.org) framework to aggregate various sources of clinical and genomic data into a common vocabulary. This conversion to a common vocabulary, technically referred to as a controlled vocabulary or ontology, allows for us to treat many sources of data as though they are one. The i2b2 structure also has support for data mappings using LOINC and RxNORM enabling the data to be stored in uniform nomenclature.

The i2b2 data model is based on the "star schema" design where each row in the main database table represents a single "fact". The facts are observations about a patient. Observations about a patient are recorded regarding a specific concept such as a lab value or medication order in the context of either an inpatient or outpatient encounter. This way of expressing a concept as an attribute in a row is known as the entity-attribute-value (EAV) model. It is very efficient to query data arranged in a star schema represented in an EAV format as a single index enables all patients' data to be searched in one query. A screen shot of our i2b2 instance is listed in Figure 1.

The i2b2 platform is used by the NIH Clinical Translational Science Award (CTSA) network, and other academic health centers. i2b2 is funded as a cooperative agreement with the National Institutes of Health. The i2b2 platform will 1) enable data sharing across institutions; 2) construct extensible frameworks; 3) be able to utilize existing client and web interfaces and 4) make use of a controlled vocabulary. Our successful experience with building an i2b2 instance in this patient population enabled the foundation for our institution's participation in the Spring 2014 awarded PCORI-funded clinical research data network (CRDN). PCORI is standardizing its data sharing initiatives on the i2b2 data structure.

To support the natural language processing needed for our analysis, we built our GI clinical phenotyping pipeline (figure 2) by modifying our existing components to develop an information extraction pipeline specific to GI phenotyping. A central component of our pipeline uses our previous work developing the Ontology Development and Information Extraction (ODIE) system for ontology based annotation of clinical documents. The ODIE toolkit encompasses a suite of services for ontology-based text annotation (OA) and ontology enrichment (OE) combined with the ODIE workbench for user interaction, analysis, and visualization. Analysis engines for OA and OE, are executed in the Unstructured Information Management Architecture (UIMA) environment, an open-source, Apache-supported component software platform for unstructured information analysis.

Our i2b2 system contains laboratory, demographics, pathology, medication (prescription) data and ICD9 diagnoses and procedure codes and annotated data. We added the genetic information on the Crohn's disease cohort. The Megascope application is displayed below:



GIANT

As part of the GI clinical phenotyping pipeline to capture those data elements that are only identifiable by domain experts, we developed a web-based annotation tool, GIANT, to enable researchers to annotate de-identified clinical reports. The application design focuses on providing users with an intelligent workspace, by displaying annotation forms and de-identified reports with the same view, automatic report queuing and providing easy access to annotation guidelines and data definitions. The application produces user statistics to report agreement between multiple annotators who are reviewing the same report. Our tool was built using the Django (www.djangoproject.com) web framework, which is an open-source project built on the Python (www.python.org) programming language. The annotation tool features include controlled user access, database support, progress reporting, task-specific error checking and a site administration interface. A screenshot of GIANT is supplied in Figure 2.

There are two output streams for GIANT. The first output is the report annotations completed by the clinical expert that will be imported into i2b2. The second output is the list of concepts identified in ODIE that appear most frequently in documents. This concept generator is used for feature selection to comprise the elements in the predictive model.

GIANT is currently supporting 24 projects throughout the health system including 5 additional projects in the Division of Gastroenterology and 11 projects in the departments of Pharmacy and Therapeutics, Radiology, and Medicine.

Ontology development and enrichment

As we began examining the operative notes that were annotated in GIANT for Crohn's disease surgery, we recognized that the operative procedure names were complex. In processing the notes through ODIE, we could not find an ontology which recognized some of the procedure names. In discussing this issue with ontology domain experts, we realized that the GI surgery domain is not well represented in standard ontologies. We added each of the procedure terms to our ontology and will contribute this ontology to the National Center for Biomedical Ontology (www.bioontology.org) upon completion. The same condition exists with identifying acute pancreatitis (AP) in radiology reports.

ODIE identifies both concepts (CUI) and semantic types (TUI) found in the narrative reports. These data will be used as the input for Technical Objective 2 (below). We used this work as a basis for our DDW 2013 submission - A Concept Recognition Tool to Identify the Surgical Complications of Crohn's Disease in Electronic Health Records. Shyam Visweswaran, Melissa I. Saul, Jeremy U. Espino, John Levander, Jason M. Swoger, Miguel Regueiro, Michael A. Dunn. The results of this study are presented in Appendix 5.

As we began to work closely with our colleagues at Walter Reed, we agreed this same approach could be used in the Military Health System since there was only access to ICD9 data to identify the surgical outcome. We agreed that we needed an approach to get more specificity from clinical reports to confirm the outcome. In the absence of operative reports, we used surgical pathology reports from the Military Health System. The technical manual we prepared for Kennell is included in Appendix 3 . We supplied them a one-time only licensed copy of De-ID to remove PHI from the surgical pathology reports before sending the reports to us. We also executed a DUA between the University of Pittsburgh and Kennell. Kennell provided the de-identified reports to Pittsburgh and we ran our ontology tool on this set of reports. We compared these ontology concepts to the concepts found in our positive set of operative notes.

The methodology we used for identifying concepts within surgical pathology reports is included in Appendix 4 along with the results of our findings at both sites.

In the AP cohort, we used the NLP pipeline for 2 purposes: a) confirming the diagnosis of acute pancreatitis beyond the use of an ICD-9 code and b) identifying the outcome of pancreatic necrosis, a condition not reliably captured by ICD-9 coding. For this analysis, we selected 150 unique patients from the overall set of AP patients identified. We selected all radiology reports of the abdomen for each patient including ultrasound, MRI, EUS, plain film and CT and loaded them into GIANT. One medicine resident and one hospitalist, under the supervision of Dr. Dhiraj Yadav annotated the reports to determine the presence or absence of AP and the presence or absence of pancreatic necrosis. A total of 2,026 (1,013 for each reviewer) reports were annotated with eight questions per report. Our findings showed that aside from the radiologist confirming the presence of the condition (440 of 2026), the second most common concept found in positive reports is the presence of psuedocysts related to pancreatitis. This work is a promising start to utilizing imaging in confirming the diagnosis of AP. Our colleagues at Walter Reed are very interested in this area and have suggested this could be an area for future collaborations.

Final Report on Technical Objective 2: Algorithm Development

In order to create variables needed for the algorithm development in both Crohn's Disease and AP cohorts, we utilized our phenotyping pipeline to classify concepts to specific outcomes and disease severities.

IBD Cohort: We have identified the specific outcome (surgery) for our Crohn's set by processing the operative reports through our phenotyping pipeline. Walter Reed's outcome variable is the surgical pathology derived outcome. The limitation with this set is that the Walter Reed reports only contained diagnosis information and no procedure or past medical history.

We performed Bayesian Network analysis using 139 single nucleotide polymorphisms (SNPs) that were measured on 332 patients with CD to test if SNPs could discriminate those that suffered from a CD-related surgical complication within 10 years from those that did not. The BN model was able to predict the occurrence of a surgical complication with an AUROC of 0.648 and accuracy of 60.24% (that performance statistics were estimated using 5-fold stratified cross-validation). We performed a similar BN analysis using 48 clinical variables for the same CD patients. The BN model's performance was statistically significantly higher with AUROC of 0.725 (accuracy of 70.42%). Finally, we performed BN analysis using both the genetic and the clinical variables and obtained an AUROC of 0.745 (accuracy of 72.24%) which is higher than using the clinical variables alone, though not statistically significantly so. The Model diagram is listed in Figure 4.

Data description

48 variables x 332 individuals (154 males, 178 females)

Outcome

- 199 with surgical complications at 10 years
- 133 without surgical complications at 10 years

Bayesian network analysis

Based on 5-fold stratified cross-validation

Area under the ROC curve = 0.725 [0.683, 0.758]
Accuracy = 70.42% [66.78%, 74.18%]]

Main predictors of outcome are:

- smoking
- dis_loc_ileal
- joint_small
- dis_loc_colorectal

AP Cohort: Initially, we identified 5970 inpatient visits for 4732 unique patients seen at our institution from 2000 to 2009 who had a primary discharge diagnosis of acute pancreatitis (AP). This was our initial study cohort. However, we did not have rich clinical data for this cohort so following IRB approval; we extended our study period to 12/31/2012. This enabled us to add an additional 1770 unique patients to the cohort.

For the AP set, we used our phenotyping pipeline to extract the vital sign data needed to construct the SIRS score along with laboratory and demographic data. The SIRS was constructed on Days 1 and 2 of the hospital stay. Using SIRS reduced our cohort to 1044 patients since not all patients had vital sign data available.

At our meeting with the Walter Reed team in April, 2013, we finalized the variables to be used in the AP model and are presented below:

Variable	**AP Patients (n = 1044)**
Age (mean +/- sd)	57.5 +/- 17.2
Males - n (%)	482 (46.2%)
Whites – n (%)	830 (79.5%)
Charleston co-morbidity Index (median, IQR)	5.3 (3.2, 6.8)
Etiology – n (%)	
Biliary	383 (36.7%)
Alcohol	132 (12.6%)
Both alcohol and biliary	37 (3.5%)
Idiopathic	209 (10.0%)
Post-ERCP	34 (3.2%)
Others	249 (23.8%)
ICU admission – n (%)	160 (15.3%)
ICU stay ≥48 hours – n (%)	130 (12.4%)
Persistent organ failure – n (%)	191 (18.3%)
Length of stay – (days) – median (IQR)	4.5 (3.1, 6.4)
Death (within days of admission) – n (%)	
7 days	12 (1.1%)
30 days	13 (1.2%)
90 days	15 (1.4%)
SIRS started on day 1 ≥2 – n (%)	318 (30.5%)
SIRS started on day 1 or 2 (within 48 hrs) ≥2 – n (%)	363 (34.8%)
SIRS started on day 2-5 – n (%)	74 (7.1%)
Persistent SIRS (i.e. >48 hours) ≥ 2 – n (%)	118 (11.3%)

We developed BN models to predict the development of persistent cardiovascular, pulmonary or renal organ failure for more than 48 hours in patients with AP. Patients with no available previous history, prior acute or chronic pancreatitis, organ transplant, pre-existing renal failure (serum Cr ≥2 or dialysis), pancreatic cancer diagnosis (within 6 months) and transfers from other institutions were excluded. This resulted in a dataset of 2102 patients of which 274 (13%) developed persistent organ failure. Persistent organ failure was defined as lasting at least 48 hours and involving the cardiovascular system (systolic blood pressure <90 mmHg), the

pulmonary system (arterial PO2 <60mm Hg at room air or the need for mechanical ventilation), and/or the kidneys (serum creatinine level >2mg/dl after rehydration or hemodialysis).

To predict persistent organ failure, we used 32 demographic, historical, and clinical and laboratory variables as potential predictors that were extracted from the EHR and were available on the first day of the ICU stay. We developed and evaluated the performance of BN models using 5-fold stratified cross-validation. The BN models were able to predict persistent organ failure with are under the **ROC curve (AUROC) of 0.77** and **accuracy of 82.45%.** Finally, we developed a single BN model from all the data (2102 patients) that is shown in Figure 5.

Final Report on Technical Objective 3: Proof-of-Principle Study

We completed an electronic review of the 339 patients who are in our NIDDK study. The electronic review was done via GIANT. We identified the patients in this cohort who also have genetic data available in our Immunochip data set. The Immunochip set represents 163 genomic regions of single nucleotide polymorphisms (SNPs) or genetic variations with at least suggestive evidence for association with either Crohn's disease, ulcerative colitis or both forms of IBD. We analyzed the data using Plink.

Our IBD cohort is defined in three separate but overlapping groups. There are 1518 individuals who had at least one surgery for Crohn's Disease. Of these 1518, 262 have at least five years of follow-up and had their disease diagnosed within ten years of first being seen at our facility and have genetic information available. We consider this to be our gold set. An additional 339 have genetic information available and at least five years of follow-up but their disease was diagnosed outside of the ten-year window for initial diagnoses. The remaining patients (n=1017) will be also be used but their analysis may be limited.

Using the 339 patients in the NIDDK cohort, we defined the outcome as one of three choices: 1) no surgery; 2) 1 surgery within 10 years of diagnosis and 3) 2 or more surgeries within 10 years of diagnosis.

Our NIDDK dataset contains 2 variables for a surgical outcome – 1) abdominal surgery captured at the time of enrollment and 2) abdominal surgery that we were able to determine using GIANT (our EHR annotation tool). The addition of the EHR data enabled us to more accurately record surgical outcomes.

For the 339 patients, we obtained genetic information for 332 of them. We have 139 SNPs. Outcomes on 332 individuals (199 with surgical complications at 10 years, 133 without surgical complications at 10 years). There were 154 males and 178 females in the dataset.

In our analysis of the genetic data, we did not find a single genetic variable that was predictive of the surgical outcome. We combined the outcome into a logical variable (having surgery or not having surgery) and redid the analysis. This gave a Bayesian network with 3 genetic variables which has an accuracy of 60% and the area under the ROC curve is 0.648. This level of predictive performance is not great but at least it shows that there is a signal in the genetic variables. Moreover, in most genetic studies of other diseases we have seen so far, the accuracy is in the 60-70% range.

We ran a second model which used the surgical outcome defined in the NIDDK registry compared to the GIANT annotation program definition of surgical outcome. There was not a significant difference. We cannot conclude that this updated information was not of value.

This SNP we discovered is in the mitogen-activated protein kinase kinase kinase 8 gene (MAP3K8). MAP3K8 activates IkappaB kinases, and thus induce the nuclear production of NF-kappaB. MAP3K8 also promotes the production of TNF-alpha and IL-2 during T lymphocyte activation.

Key Research Accomplishments

ABSTRACTS PRESENTED AT NATIONAL MEETINGS
AASLD, American Association for the Study of Liver Diseases
DDW, Digestive Diseases Week

AASLD 2012 Current Spectrum of Liver Disease in Inflammatory Bowel Disease Michael A. Dunn, Claudia M. Ramos Rivers, Amy R. Schmotzer, Miguel D. Regueiro, Kapil B. Chopra, David G. Binion

AASLD 2013 Body Composition In Cirrhotic Patients After Liver Transplantation Joseph T Bergerson, June-Goo Lee, Alessandro Furlan, Achuthan Sourianarayanane, Amit D. Tevar, Andrea F. DiMartini, Michael A. Dunn

DDW 2013 A Concept Recognition Tool to Identify the Surgical Complications of Crohn's Disease in Electronic Health Records. Shyam Visweswaran, Melissa I. Saul, Jeremy U. Espino, John Levander, Jason M. Swoger, Miguel Regueiro, Michael A. Dunn

DDW 2013 Electronic Health Record Information is Useful to Predict Clinically Relevant Outcomes in Acute Pancreatitis (AP). Dhiraj Yadav, Melissa I. Saul, Georgios I. Papachristou, David C. Whitcomb, Shyam Visweswaran, Michael A. Dunn.

DDW 2013 Inflammatory Bowel Disease and Selective Immunoglobulin a Deficiency. Eric J. Vargas, Claudia M. Ramos Rivers, Miguel Regueiro, Arthur Barrie, Leonard Baidoo, Marc Schwartz, Jason M. Swoger, Michael A Dunn, Anwar Dudekula, David G. Binion

DDW 2013 Effect of the Bile Acid Sequestrant Colesevelam on Health Related Quality of Life in Crohn's Disease. Chandraprakash Umpathy, Claudia M. Ramos Rivers, Miguel Regueiro, Leonard Baidoo, Arthur Barrie, Marc Schwartz, Jason M. Swoger, Michael A. Dunn, Katherine A. Weyant, Andrew R. Watson, David G. Binion.

DDW 2013 Silent Crohn's Disease: Elevated C Reactive Protein in Asymptomatic Patients and Risk of Subsequent Hospitalization. Eric J. Vargas, Claudia M. Ramos Rivers, Miguel Reguerio, Leonard Baidoo, Arthur Barrie, Marc Schwartz, Jason M. Swoger, Matthew Coates, Michael a. Dunn, Anwar Dudekula, David G. Binion.

DDW 2013 Sleep Disturbance and the Clinical Course of IBD. Claudia M. Ramos Rivers, Eric J. Vargas, David G. Binion, Miguel Regueiro, Leonard Baidoo, Arthur Barrie, Jason M. Swoger, Marc Schwartz, Michael A. Dunn, Eva Szigethy, David Benhayon.

DDW 2013 Clinical Factors Contributing to Abdominal Pain in IBD. Claudia M. Ramos Rivers, Eric J. Vargas, Matthew Coates, Miguel Regueiro, Michael a. Dunn, Jason M. Swoger, Marc Schwartz, Arthur Barrie, Leonard Baidoo, Eva Szigethy, David G. Binion

DDW 2013 Metabolic Syndrome and Inflammatory Bowel Disease. Jennifer L. Seminerio, Claudia M. Ramos Rivers, Jaideep Behari, Annette Wilson, Katherine A. Weyant, Miguel Regueiro, Leonard Baidoo, Arthur Barrie, Jason M. Swoger, Marc Schwartz, Michael A. Dunn, David G. Binion.

DDW 2014 Clinical Characteristics of Inflammatory Bowel Disease (IBD) Patients Who Call After Hours Claudia M. Ramos Rivers[1], Miguel Regueiro[1], Michael A. Dunn[1], Eva Szigethy[2, 1], Marc Schwartz[1], Arthur Barrie[1], Jana G. Hashash[1], Jason M. Swoger[1], Leonard Baidoo[1], David G. Binion[1]

DDW 2014 Association of Telephone Activity With Clinical Features in Inflammatory Bowel Disease (IBD): a Prospective Validation Study. Claudia M. Ramos Rivers[1], Miguel Regueiro[1], Michael A. Dunn[1], Eva Szigethy[2, 1], Jana G. Hashash[1], Marc Schwartz[1], Arthur Barrie[1], Leonard Baidoo[1], Jason M. Swoger[1], David G. Binion[1]

DDW 2014 Characterization of Autonomic Dysfunction in Inflammatory Bowel Disease (IBD): Prospective Use of a Short Self-Assessment Instrument for Screening in a Tertiary Referral Clinic. Claudia M. Ramos Rivers[1], Kimberly Baker[1], Jana G. Hashash[1], Miguel Regueiro[1], Eva Szigethy[2, 1], David J. Levinthal[1], Michael A. Dunn[1], David G. Binion

DDW 2014 Impact of Benign Joint Hypermobility Syndrome on Inflammatory Bowel Disease Nitin Aggarwal[2], Kimberly Baker[1], Claudia M. Ramos Rivers[1], Jana G. Hashash[1], Miguel Regueiro[1], Michael A. Dunn[1], David G. Binion[1]

DDW 2014 Patterns of Antibiotic Exposure and Clinical Disease Activity in Inflammatory Bowel Disease: a 4 Year Prospective Study Jana G. Hashash, Claudia M. Ramos Rivers, Miguel Regueiro, Arthur Barrie, Marc Schwartz, Leonard Baidoo, Jason M. Swoger, Michael A. Dunn, David G. Binion

DDW 2014 The Longitudinal Impact of Serotonin Reuptake Inhibitors on Quality of Life and Disease Activity in Adults with Inflammatory Bowel Disease (IBD). Claudia M. Ramos Rivers[1], David G. Binion[1], Ada Youk[3], Miguel Regueiro[1], Michael A. Dunn[1], Jana G. Hashash[1], Marc Schwartz[1], Leonard Baidoo[1], Arthur Barrie[1], Jason M. Swoger[1], Eva Szigethy[2, 1]

DDW 2014 Prospective Analysis of Bile Acid Sequestrant Therapy in Inflammatory Bowel Disease Chandraprakash Umapathy[1], Claudia M. Ramos Rivers[2], Miguel Regueiro[2], Arthur Barrie[2], Jana G. Hashash[2], Marc Schwartz[2], Jason M. Swoger[2], Leonard Baidoo[2], Michael A. Dunn[2], David G. Binion[2]

DDW 2014 Unconjugated Hyperbilirubinemia Is Inversely Associated With Modified Hepatitis Activity Index in Chronic Hepatitis C Su1024 | Achuthan Sourianarayanane, Amy Schmotzer, Kapil Chopra, Michael A. Dunn

PAPERS PUBLISHED

Juneja M, Baidoo L, Schwartz MB, Barrie A 3rd, Regueiro M, Dunn M, Binion DG. Geriatric inflammatory bowel disease: phenotypic presentation, treatment patterns, nutritional status, outcomes, and comorbidity. Dig Dis Sci. 2012; Sep;57(9):2408-15. PMID 22359191

Dunn MA, Behari J, Rogal SS, O'Connell MR, Furlan A, Aghayev A,Gumus S, Saul MI, Bae KT. Hepatic steatosis in diabetic patients does not predict adverse liver-related or cardiovascular outcomes. Liver International, 2013, 33(10):1575-1582. PMID 23944954

Ramos-Rivers C, Regueiro M, Vargas EJ, Szigethy E, Schoen RE, Dunn MA, Watson AR, Schwartz M, Swoger J, Baidoo L, Barrie A, Dudekula A, Youk AO, Binion DG. Telephone activity in the care of inflammatory bowel disease. Clin Gastroenterol Hepatol, 2014; 12:986-994. PMID 24262938

PAPERS IN REVIEW

Bergerson JT, Lee JG, Furlan A, Sourianarayanane A, Fetzer DT, Tevar AD, Landsittel DP, DiMartini AF, Dunn MA. Liver Transplantation Arrests and Reverses Muscle Wasting.

Visweswaran, S. Saul, M. Morris M, Espino JU, Levander J, Swoger JM, Regueiro M, Dunn MA. Automated Identification of Complex Phenotypes in Electronic Health Records

Seminerio JL, Ramos-Rivers C, Hashash JG, Regueiro M, Baidoo L, Barrie A, Swoger J, Schwartz Weyant MK, Dunn MA, Binion DG. Impact of Obesity on Inflammatory Bowel Disease: Metabolic, Clinical and Therapeutic Implications

Vargas EJ, Ramos-Rivers C, Hashash JG, Regueiro M, Watson A, Dunn MA, Schwartz M, Swoger J, Baidoo L, Barrie AM, Binion DG. Silent Crohn's Disease: Asymptomatic Patients With Elevated CRP Are at Risk for Subsequent Hospitalization

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Reportable Outcomes

- Coordinated face-to-face research meetings in Pittsburgh for Walter Reed and Pittsburgh co-investigators on April 27, 2012 and April 19, 2013.
- Held online project meeting with Pittsburgh and Walter Reed team on October 25, 2013.
- Submitted new proposal to the Congressionally Directed Medical Research Program (W81XWH-13-PRMRP-TTDA) to continue our work.
- Collaborated with Kennell to explore the feasibility of using a de-identification software program to remove PHI in clinical narrative reports and do concept extraction on the de-identified set to enable predictive modeling. This was one of the first projects that Kennell did with textual reports from the Military Health System.

Conclusions

We assembled a collaborative team from both gastroenterology and informatics. We have built our infrastructure according to plan. We were able to develop a data harmonization process for 2 diseases – Crohn's and Acute Pancreatitis between two very different health care systems. We have shown that we can share data. We have enabled Bayesian network analysis to be done on these two data sets. For this initial working effort between the two groups, we have built a robust and repeatable process to study additional diseases.

Figures

Figure 1 - i2b2 Query Tool

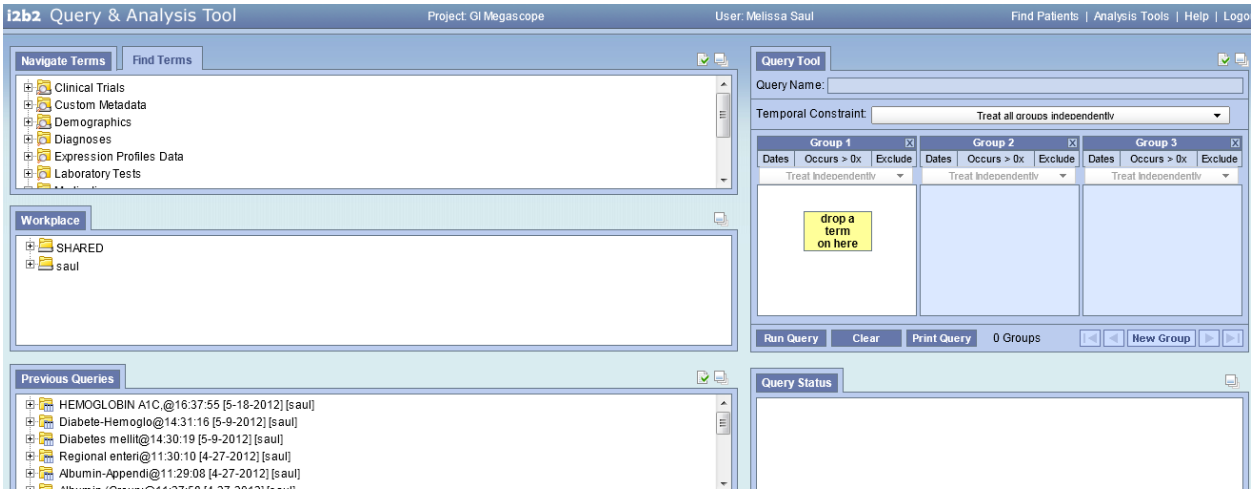


Figure 2 – GIANT user interface

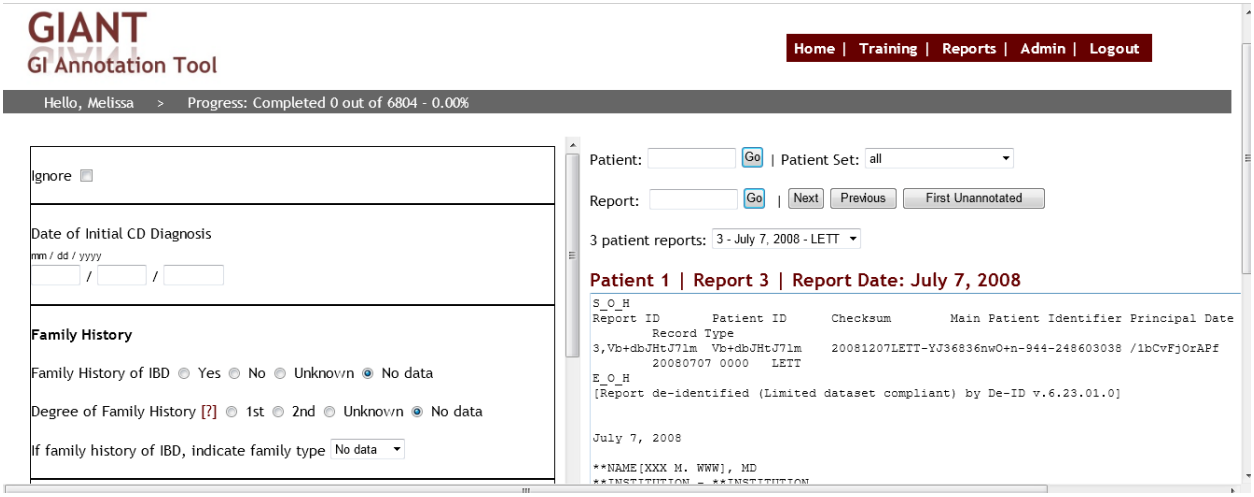


Figure 3 – GI Clinical Phenotyping Pipeline

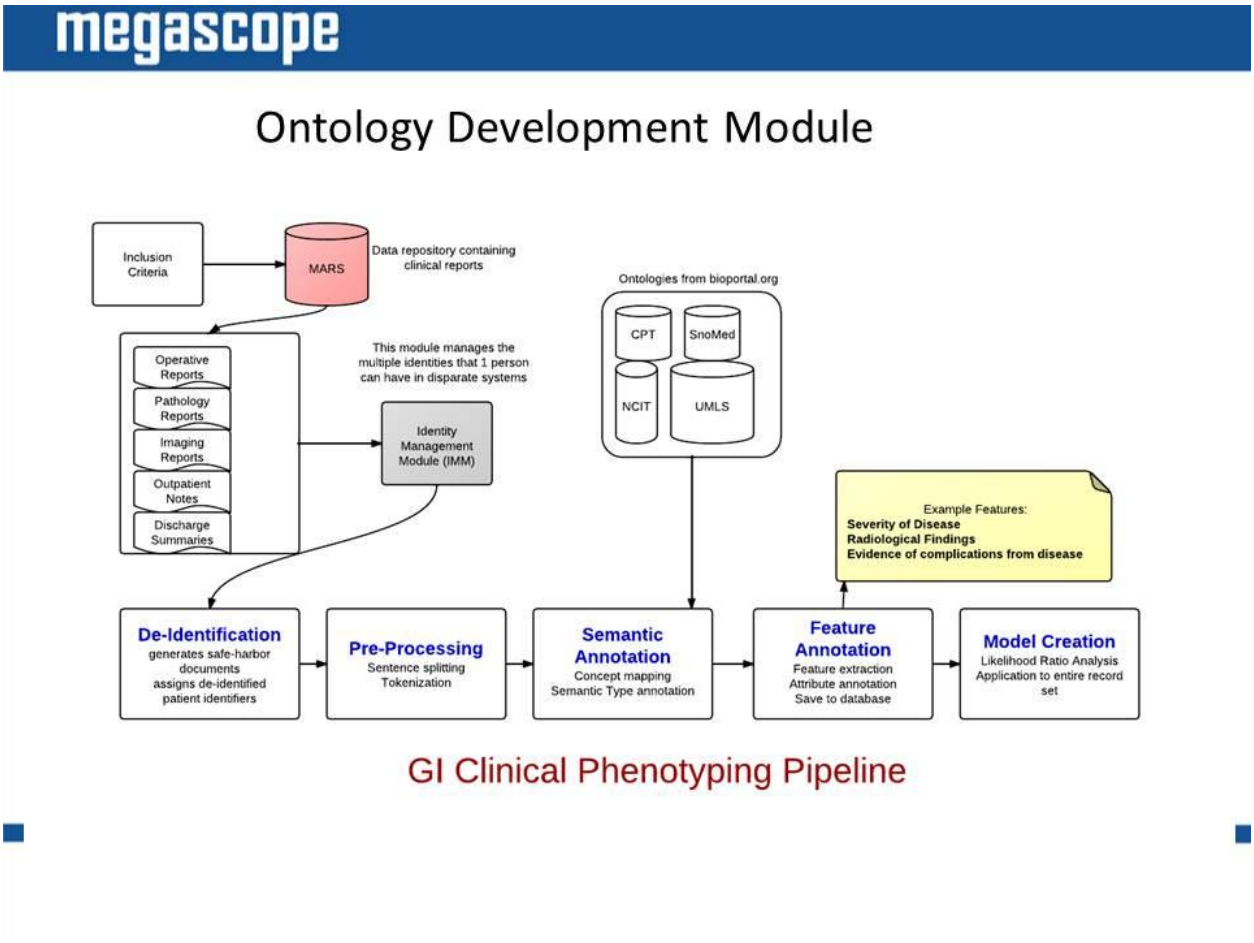


Figure 4 – Bayesian Network for CD Outcomes

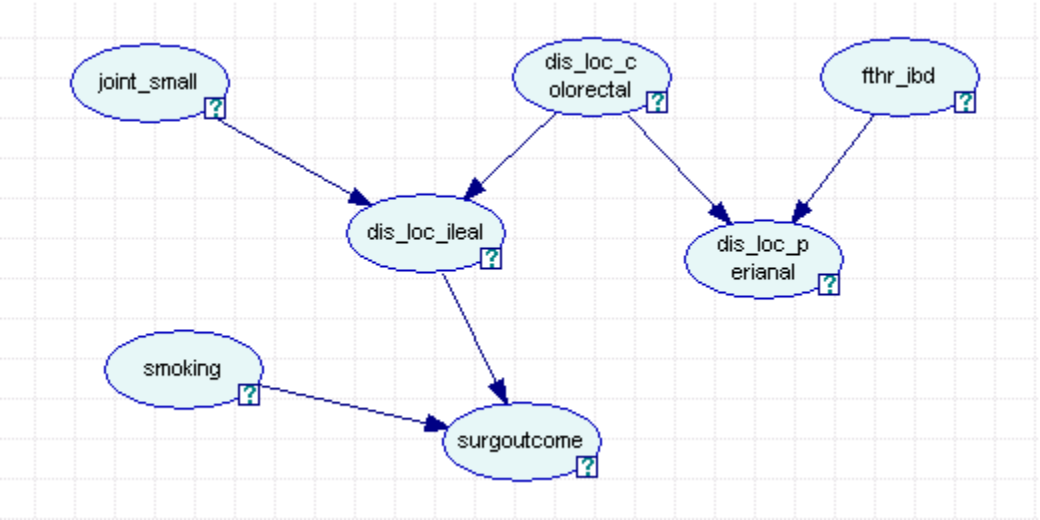
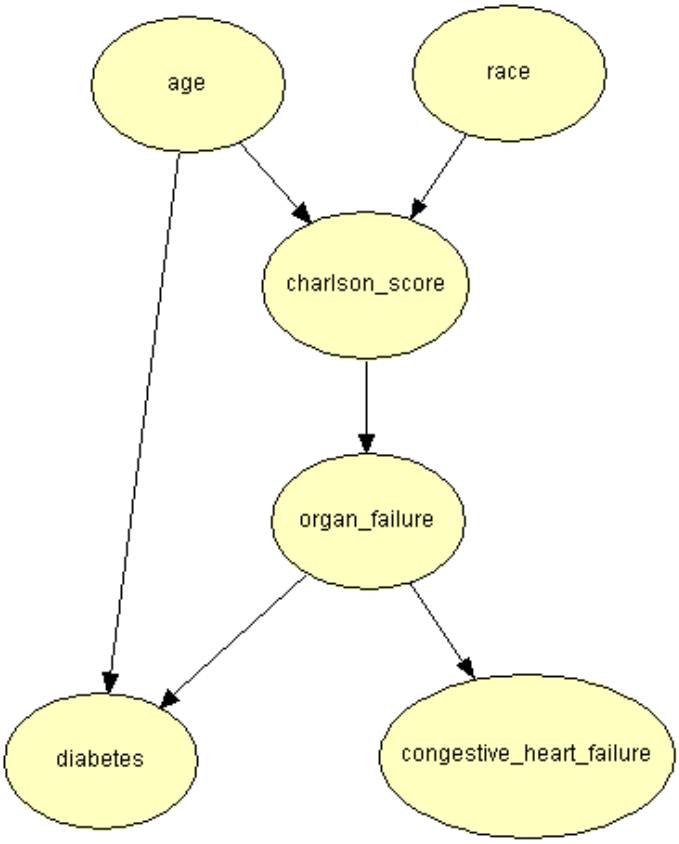


Figure 5 – Bayesian Network for AP Outcomes



Appendices

Appendix 1 – Agenda for April 19, 2013 Joint Meeting

Framework for Smart Electronic Health Record Linked Predictive Models to Optimize Care for Complex Digestive Diseases Project

Hosted by: University of Pittsburgh Department of Biomedical Informatics (DBMI)
April 19, 2013

I. Status Report of CD and AP Projects – All

II. AP Project Review – Dhiraj Yadav, MD, MPH

III. Bayesian Modeling Methods Workshop – Shyam Visweswaran, MD, PhD
   a. Report on Pittsburgh CD Cohort with genetic data modeling
   b. Hugin software demo

IV. Next Steps

Meeting Information

Location: Department of Biomedical Informatics
5607 Baum Blvd., 5th floor
Pittsburgh, PA 15261

There is a sign indicating DBMI Office Entrance in front of building. The building looks like a construction zone. There is an Aldi's Grocery Store in one corner of the building.

Parking: Parking lot is across the street in abandoned parking lot. Labeled as DBMI Parking

Contact Info

Melissa Saul – 412-818-5448 (cell)

De-identification and term classification process description for Kennell Inc.

4/24/2014

John Levander

jdl50@pitt.edu

Process Overview:

1. DBMI supplies the De-ID software to Kennell Inc.
2. Kennell extracts the data to be de-identified into a single text file (referred to in this document as deid-input.txt) in the format expected by De-ID.
3. Kennell runs the De-ID software on the deid-input.txt file. The software will output a deid-input.deid file, which is a copy of the original text file with PHI removed. The De-ID software will also output a "linkage" file, and a log file.
4. Kennell supplies DBMI with the deid-input.deid file. DBMI is also requesting the deid-input.deid.log file for debugging purposes. The deid-input.deid.log file does not contain PHI.
5. DBMI will use software to identify UMLS terms (using the NCI dictionary) in the deid-input.deid file and build a "terms list" for each report.
6. DBMI will supply Kennell with the "terms list" in a text file in csv format.

How to build a De-ID input file:

Import the data to be de-identified, using the expected De-ID format, into the file named deid-input.txt. In short, the De-ID format consists of the token S_O_H followed by a bar-delimited header, followed by the token E_O_H, followed by the text of the clinical note, followed by the token E_O_R. The bar-delimited header should contain a uniquely identifying document id in the first field, the patient identifier in the second field, the patient name in the third field (if available), and the provider name in the 7th field (if available). The De-ID input file format is described in-depth in the User Manual found in the program directory of the De-ID software.

How the deid-input.txt example file was built:

The deid-input.txt example file used record 1 and 2 from the "Sample Pathology Results with PHI removed.xlxs" file. The DOCUMENT_ID was placed in the first header field, and the PATSSN was placed in the second header field. The rest of the header fields were left blank. This is a screenshot of the first two records, in the De-ID input file format, in the deid-input.txt file:

```
S_O_H
175047928|252918048||
E_O_H


A. STOMACH, ANTRUM GREATER CURVATURE, BIOPSY:
 - ANTRAL TYPE GASTRIC MUCOSA WITH MILD CHRONIC INACTIVE GASTRITIS.
 - NO HELICOBACTER PYLORI-LIKE ORGANISMS IDENTIFIED.


B. STOMACH, BODY DISTAL GREATER CURVATURE, BIOPSY:
 - OXYNTIC TYPE GASTRIC MUCOSA WITH PROTON PUMP INHIBITOR EFFECT.
 - NO HELICOBACTER PYLORI-LIKE ORGANISMS IDENTIFIED.


C. STOMACH, BODY PROXIMAL GREATER CURVATURE, BIOPSY:
 - OXYNTIC TYPE GASTRIC MUCOSA WITH PROTON PUMP INHIBITOR EFFECT.
 - NO HELICOBACTER PYLORI-LIKE ORGANISMS IDENTIFIED.


D. STOMACH, FUNDUS, BIOPSY:
 - FUNDIC GLAND POLYP.


E. STOMACH, ANTRUM LESSER CURVATURE, BIOPSY:
 - INTESTINAL METAPLASIA.
 - NEGATIVE FOR DYSPLASIA.


F. STOMACH, ANGULARIS, BIOPSY:
 - INTESTINAL METAPLASIA.
 - NEGATIVE FOR DYSPLASIA.


G. STOMACH, BODY LESSER CURVATURE, BIOPSY:
 - OXYNTIC TYPE GASTRIC MUCOSA WITH PROTON PUMP INHIBITOR EFFECT.
 - NO HELICOBACTER PYLORI-LIKE ORGANISMS IDENTIFIED.

E_O_R

S_O_H
179497991|873775832||
E_O_H
VAGINAL-CERVICAL CYTOLOGIC MATERIAL:
      SATISFACTORY FOR EVALUATION, ENDOCERVICAL COMPONENT IDENTIFIED.
      SPECIMEN CONTAINS PARTIALLY OBSCURING BLOOD AND INFLAMMATION.
      NEGATIVE FOR INTRAEPITHELIAL LESION OR MALIGNANCY.
      The Pap test is only a screening test.  False negative results can
      occur.  Regularly scheduled Pap tests are recommended.

E_O_R
```

The third report in the deid-input.txt file is an example clinical note from the internet. This note has fake PHI, and was included to demonstrate the de-identification features of the De-ID software. The

following image is a screenshot of the third report in the file:

S O H
6293895807 123456789
E_o_H
Pa ien Informa ion

Name: Monica La e Home Phone: 444-444-4444
Addregg: 4444 Coffee Ave
Chocola e. California Office Phone:
Pa ien I : 0000-44444 Fax:
Birh Dae: 04/04/1950 S a ug: Ac ive
Gender: Female Mari al S a ug: ivorced
Con acBy: Phone Race: Black
asf Sec No: 444-444-4444 Language: Engligh
: Carl MRN: MR-111-1111
Referred by: · S a ug: Full- ime
Email: Char : No
Home LOC: IeServeEveryone Ex ernal ID: MR-111-1111
Problemg

DIABETES MELLITUS (ICD-250.)
HYPERTENSION, BENIGN ESSENTIAL (ICD-401.1)

Medica iong

PRINIVIL TABS 20 MG (LISINOPRIL) 1 po
LagRefill: t30 x 2 : CarlMD (08/27/2010)
HUMULIN INJ 70/30 (INSULIN REG & ISOPHANE (HUMAN)) 20 unig breakfag
LagRefill: t600x O : CarlMD (08/27/2010)

Direc iveg

Allergieg and Adverge Reac iong (! cri ical)

Serviceg Due

FLU VAX, PN:::UMOVAX, MICROALB URN

3/18/2011 - Office Vigi: F/Diabe eg
Provider: CarlMD
Loca ion of Care: rleServeEveryone Clinic

OFFICE VISIT

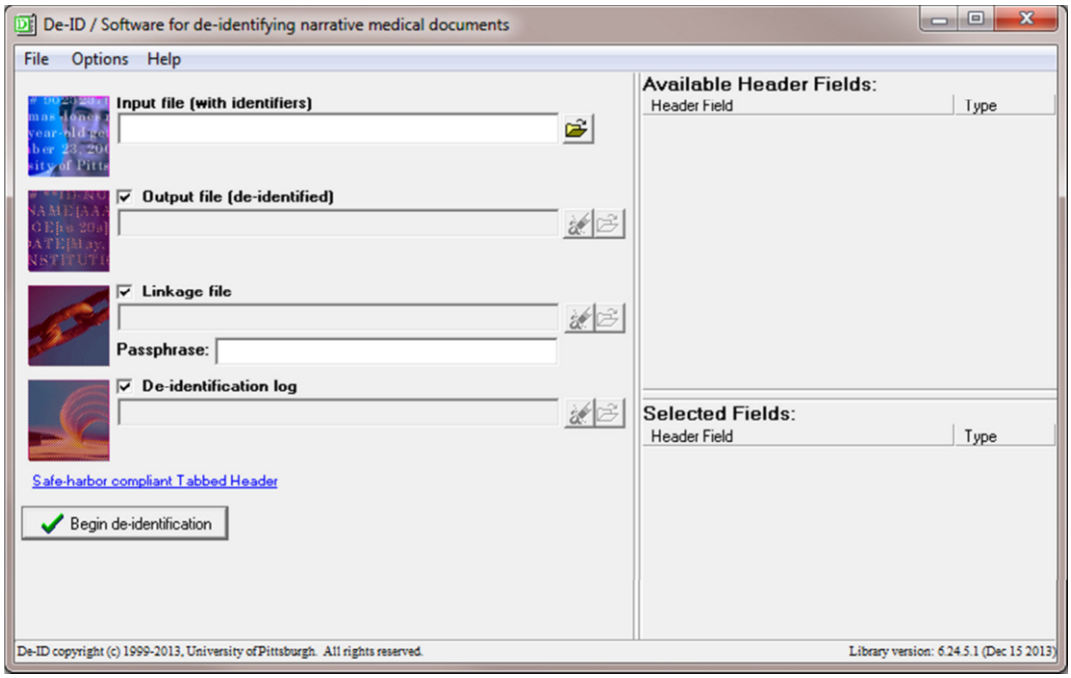
Hig ory of Pregen Illnegg
Reagen for vigi: Rou ine follow up
Chief Complain: No complain g

Hig ory

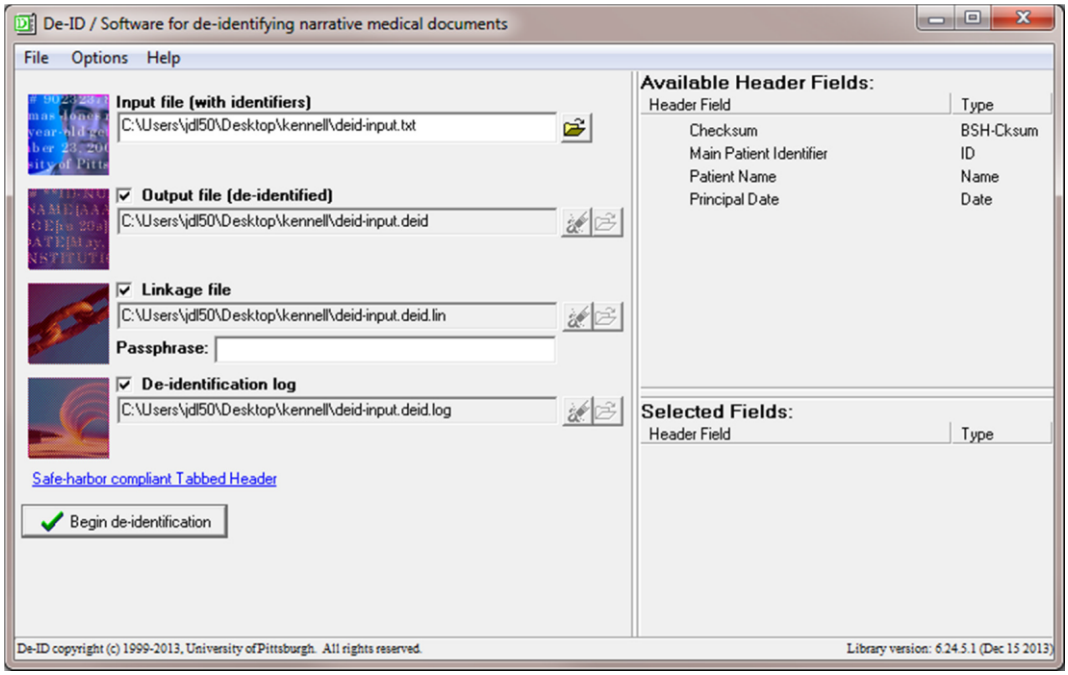
Diabe eg Managemen
g;t,x6iW6i Symp omg
;!..:no
;t,xsUe:no
Blurred vigion: no

How to run the de-identifier

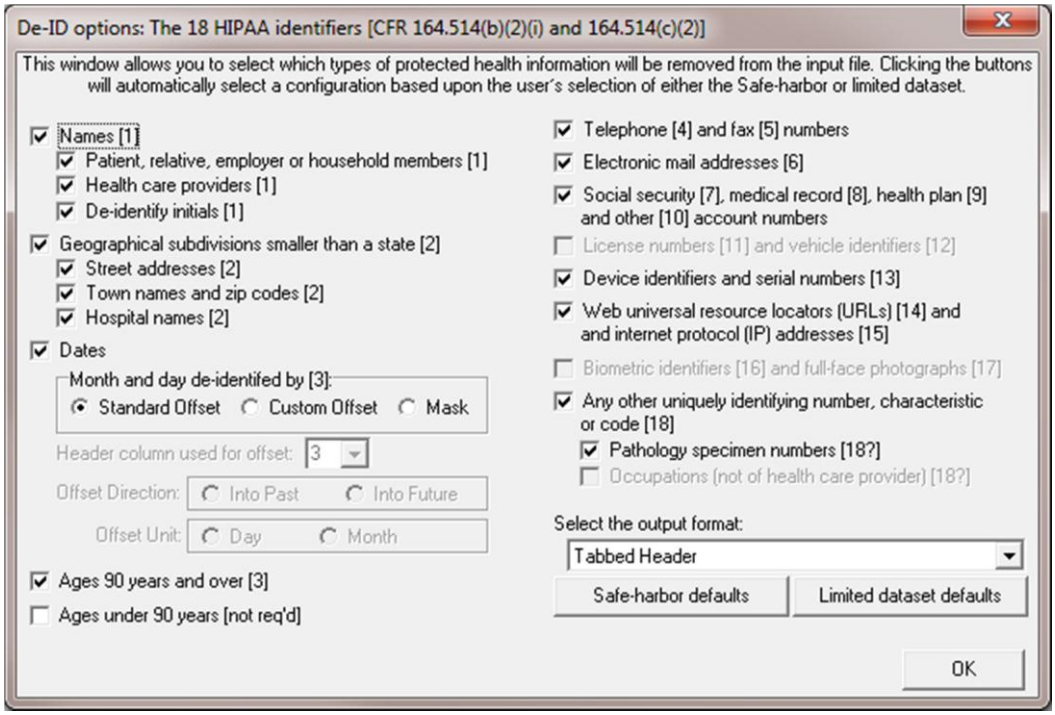
Start De-ID. The following screen is displayed:



Click the folder button in the top center of the screen, next to the "Input file" text box. That opens an "Open File..." dialog. Select the "deid-input.txt" file that we built in Step 1.

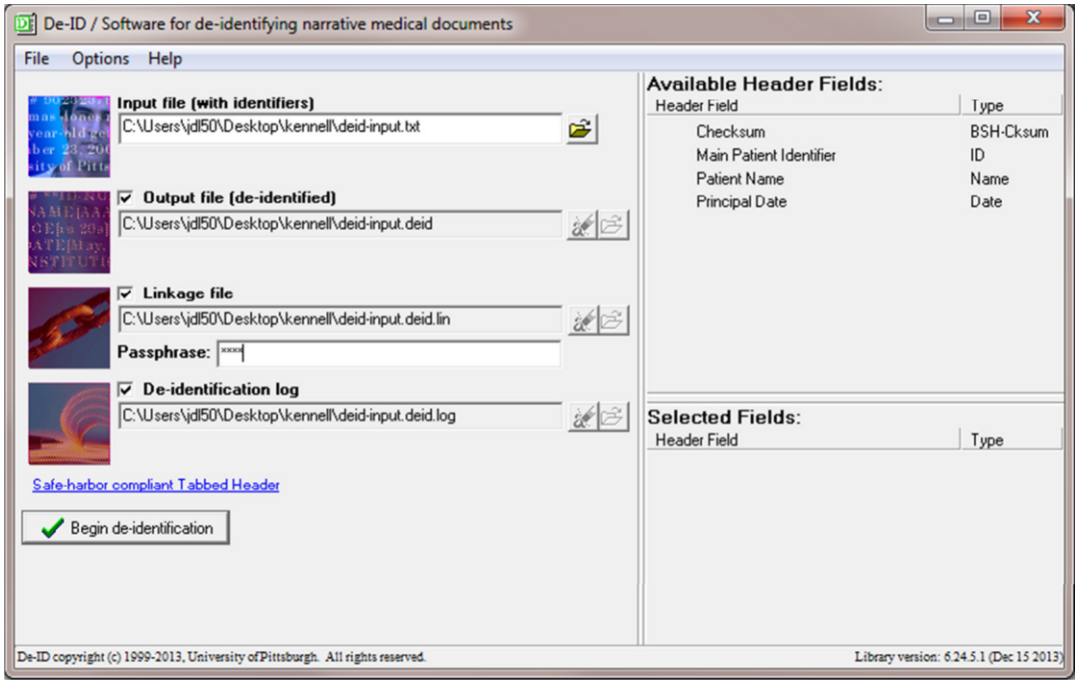


Next, open the configuration dialog by selecting "Options->De-identification/output options" from the menu.



Select "Tabbed Header" as the output format, and click the button "Safe-harbor defaults." Press "OK."

Next, enter the phassphrase for the linkage file. In the example provided, the passphrase "test" was used.



Finally, click "Begin de-identification."

Review the output files

Open the output file, ***deid-input.deid,*** and review the de-identified results. **This is the file that will be supplied to DBMI.** In the screenshot below, we show report 2 and some of report 3 in its de-identified form. Notice that the DOCUMENT_IDs and the PATSSNs have been encrypted so they can't be linked back to the original document:

```
S O H
 eporc ID   Pacienc ID
2,iaMCvJxrwYeV   iaMCvJxrwYeV
E O H
[eporc de-idencified (Safe-compliant;)        by De-ID v.6.24.5.1]

VAGINAL-CE VICAL CYTOLOGIC MATE IAL:
       SATISFACTOY FOEVALUATION,    ENDOCE VICAL COMPONENT I ENTIFIED.
       SPECIN CONTAINS   P TIALLY OBSCURING BLOOD AND INFLAMMATION.
       NEGATIVE FOINTRAEPITHELIAL LESION OMALIGNANCY.
       The Pap cesc is only a screening cesc.  False negacive resulcs can
       occur.   egularly scheduled Pap cescs are recommended.



E O_R

S O H
 eporc ID   Pacienc ID
3,9808HYCOBHMq   9808HYCOBHMq
E O H
[eporc de-idencified (Safe-compliant;)        by  e-ID v.6.24.5.1]

Pacienc Informacion

Name: ⁴⁴NAME[AAA BBB]   Home Phone: ⁴⁴PHONE
-⁴STREET-ADD::tESS
               Chocolace, California   Office Phone:
Pacienc ID: ••I -NOM    Fax:
Birch Dace: ⁴⁴DATE[Nov 04 1950] Scacus: Accive
Gender: Female  Marical Scacus: Divorced
Concacc By: Phone    ace:Black
Sec No:     ••PHONE Language: English
     ⁴⁴NAME[ZZZ: YYY XXX]  M  : M -··PHONE
 eferred by:   -    Scacus: Full-cime
Email:  Charc:      No
Home LOC:rleServeEveryone    Excernal ID: M -··PHONE
Problemg

DIABETES MELLITUS (IC -250.)
HYPERTENSION, BENIGN ESSENTIAL (ICD-401.1)

Medicacions

P INIVIL TABS 20 MG (LISINOP IL) 1 po
Lase  efill: #30 x 2 : ⁴⁴NAME[YYY XXX] MD (⁴⁴ ATE[Mar 27 2011])
```

Next, examine the deid-input.deid.log file which looks as follows:

```
==========
Study ID: 1,Xdlh4U12tgDR Report Type:
----------

==========
Study ID: 2,iaMCvJxrwYeV Report Type:
----------

==========
Study ID: 3,98O8HYCOBHMq Report Type:
----------
Name: **NAME[AAA BBB]
Home Phone: **PHONE
**STREET-ADDRESS
Patient ID: **ID-NUM
Birth Date: **DATE[Nov 04 1950]
Soc Sec No: **PHONE
Resp **NAME[ZZZ: YYY XXX]
MRN: MR-**PHONE
External ID: MR-**PHONE
Last Refill: #30 x 2 : **NAME[YYY XXX] MD (**DATE[Mar 27 2011])
Last Refill: #600 u x 0 : **NAME[YYY XXX] MD (**DATE[Mar 27 2011])
**DATE[Oct 18 2011] - Office Visit: F/u Diabetes
Provider: **NAME[YYY XXX] MD
**INSTITUTION
**INSTITUTION
**DATE[Oct 24 2011]
**STREET-ADDRESS California
**ID-NUM
Fax: **PHONE
**INSTITUTION
**DATE[Oct 24 2011]
**STREET-ADDRESS California
**ID-NUM
Fax: **PHONE
**DATE[Oct 18 2011] - Lab Report: Metabolic Panel Provider: **NAME[YYY XXX] MD
**INSTITUTION
**DATE[Oct 24 2011]
**STREET-ADDRESS California
**ID-NUM
Fax: **PHONE
DOB: **DATE[Nov 04 1950] **ID-NUM
Date **DATE[Oct 18 2011] HEIGHT (in) 64 WEIGHT (lb) 140 TEMPERATURE (deg F) 98 TEMP SITE oral PULSE RATE (/min) 72 PULSE RHYTHM
```

This file is a listing of all text that was de-identified. It contains no PHI.

What DBMI will do with the .deid file, and what will be returned to Kennell

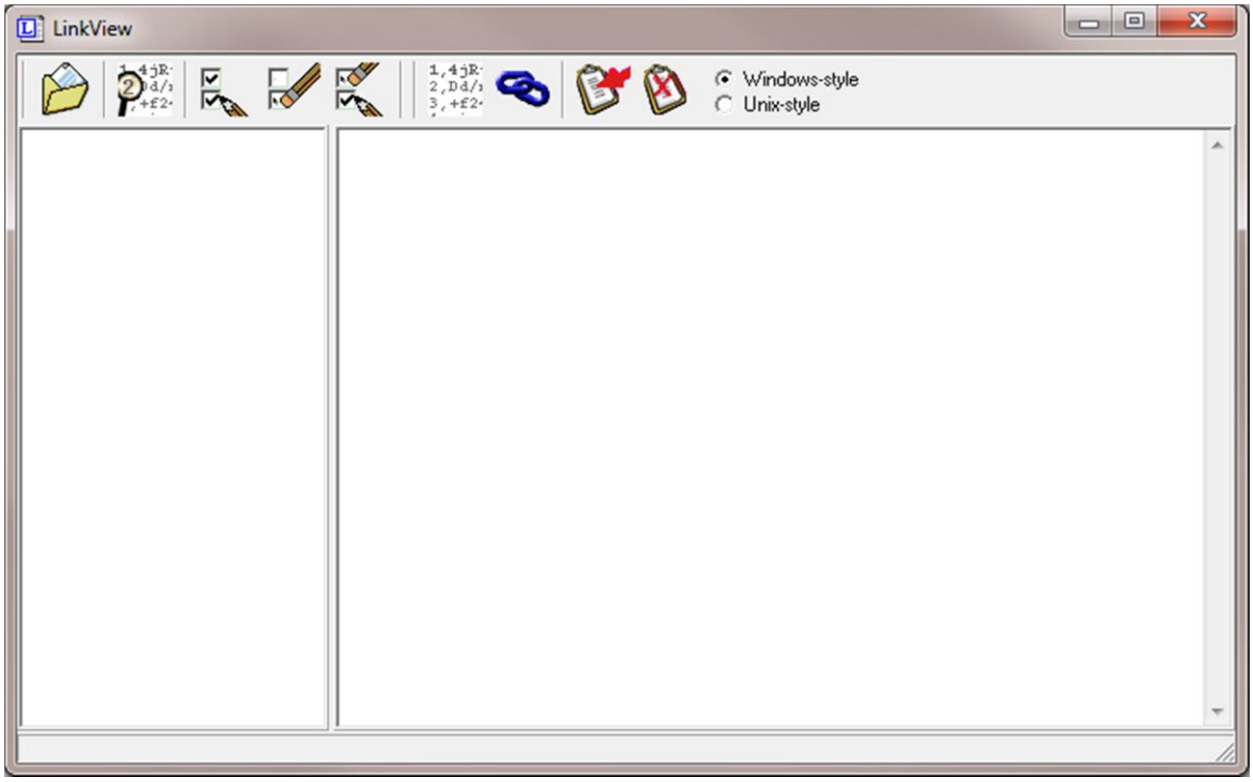
DBMI will take the deid-input.deid file and extract the terms within the file. DBMI will supply Kennell with this "terms list" in the following format:

```
"Report,Matched Term,Code,Name,Semantic Type,Annotations,Acronym,Negated"
"3,9808HYCOBHMq,Report,C0684224,Report (document),Intellectual Product,Report/7,7,"
"3,9808HYCOBHMq,Patient,C0030705,Patient,Patient or Disabled Group,Patient/17"
"3,9808HYCOBHMq,Date,C0011008,Date in time,Temporal Concept,Date/38"
"3,9808HYCOBHMq,Principal,C0205225,Principal,Qualitative Concept,Principal/28"
"3,9808HYCOBHMq,ID,C0020787,Idaho (geographic location),Geographic Area,ID/14"," ID/25"
"3,9808HYCOBHMq,CHIEF COMPLAINT,C0277786,Chief complaint (finding),Finding,CHIEF/181"," COMPLAINT/187"
"3,9808HYCOBHMq,OP POST DIAGNOSIS,C1318969,Post-op diagnosis,Finding,OP/201", POST/204, OP/209," DIAGNOSIS/212"
"3,9808HYCOBHMq,PRE OP DIAGNOSIS,C1318968,Pre-op diagnosis,Finding,PRE/197", OP/201, OP/209," DIAGNOSIS/212"
"3,9808HYCOBHMq,Regional enteritis NOS,C0678202,Regional Enteritis,Disease or Syndrome,Regional/223", enteritis/232," NOS/242"
"3,9808HYCOBHMq,Crohn's,C0010346,Crohn's Disease,Disease or Syndrome,Crohn's/247"
"3,9808HYCOBHMq,small bowel obstruction,C0235329,Small bowel obstruction,Disease or Syndrome,small/274", bowel/280," obstruction/286"
"3,9808HYCOBHMq,revision,C0439617,Revision,Temporal Concept,revision/319"
"3,9808HYCOBHMq,pouch,CL333395,Pouch,Medical Device,pouch/313"
"3,9808HYCOBHMq,history,C0019665,history,Intellectual Product,history/299"
"3,9808HYCOBHMq,disease recurrent,C0277556,Recurrent Disease,Disease or Syndrome,disease/255"," recurrent/264"
"3,9808HYCOBHMq,PROCEDURE,C2700391,Procedure,Activity,PROCEDURE/329"
"3,9808HYCOBHMq,end,C1272693,End,Qualitative Concept,end/356"
"3,9808HYCOBHMq,construction,C0079326,Facility Construction,Classification,construction/340"
"3,9808HYCOBHMq,CLINICAL,C0205210,Clinical,Qualitative Concept,CLINICAL/379"
"3,9808HYCOBHMq,QUESTION,C1522634,Question,Conceptual Entity,QUESTION/388"
```

This example is populated with dummy data, but note that the Report id in the first column matches the encrypted report id of the third report in the deid-input.deid file. The next section explains how to "link" these encrypted report ids back to the original reports.

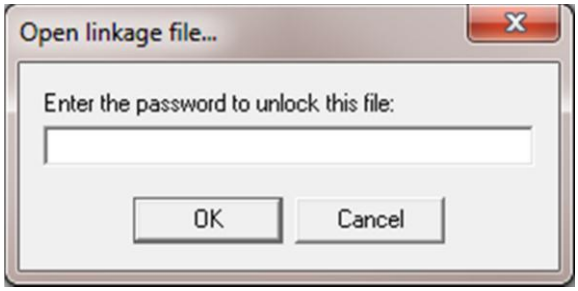
View the linkage file:

Start the LinkView program.



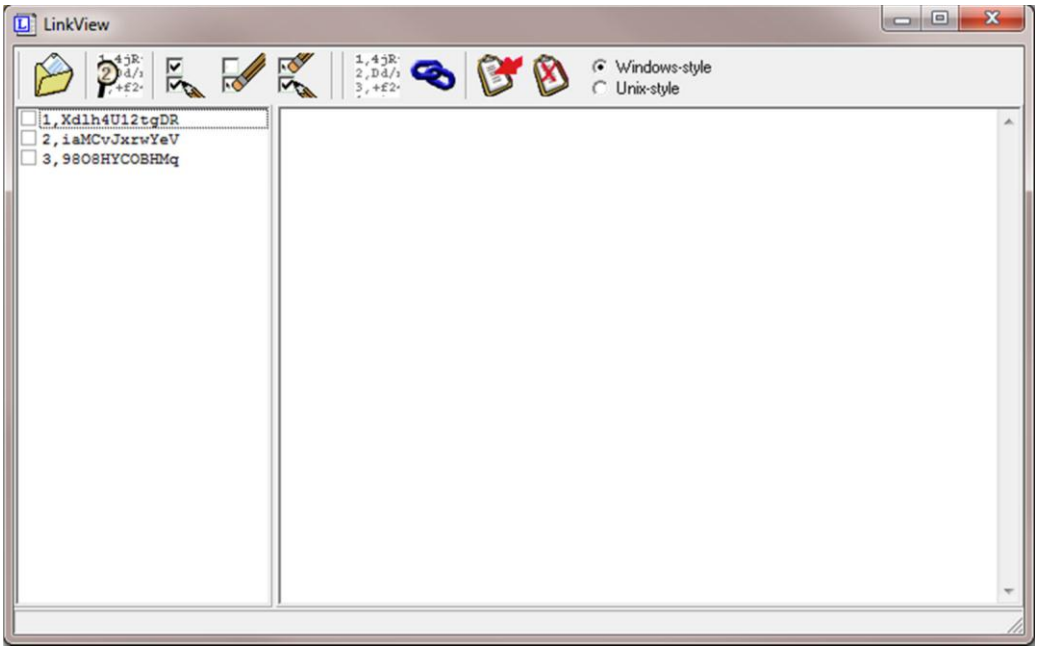
Next, click the envelope icon in the upper left hand corner. This opens an "Open file..." dialog. Select the file "deid-input.deid.lin" and press the "Open" button.

You will be prompted for the password. The example linkage file uses the password "test"

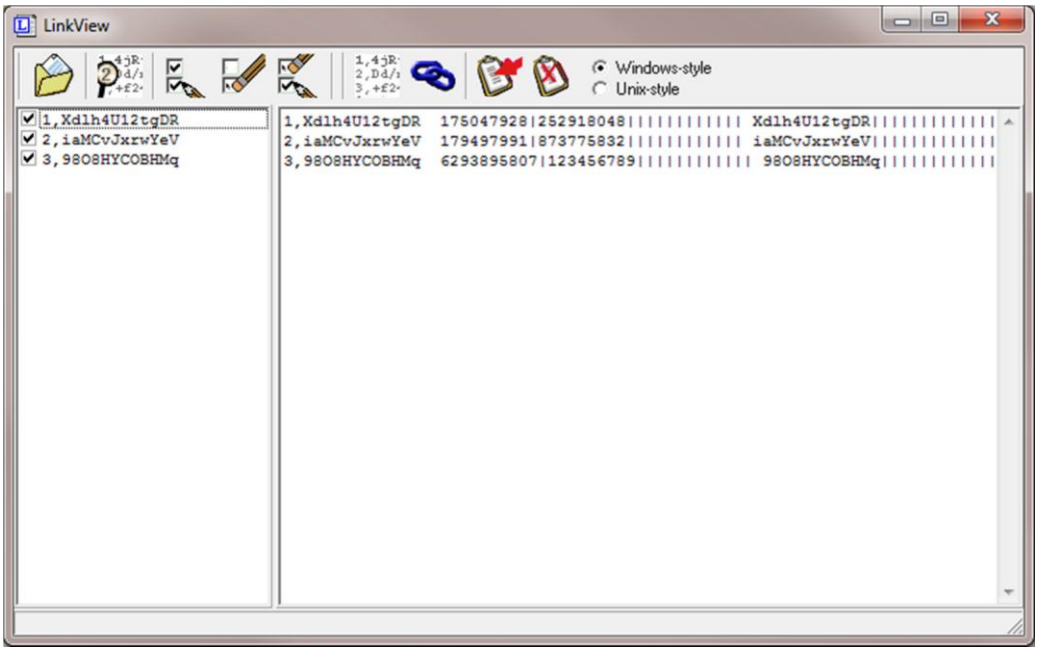


Enter the password and press OK.

The following screen appears:



Put a check in each of the checkboxes and press the chain (linkage) icon. This shows the de-identified report id's AND the original header of the clinical notes.



Clicking the "copy to clipboard" button will place the contents of the linkage file in the clipboard.

Appendix 3 – Methodology for Analysis of Kennell Reports and Program Results

Methodology for Processing of Surgical Pathology Reports received from Kennell

Background

Inclusion criteria for Kennell set of reports

- 2,349 reports that were previously identified by Kennell as being part of the Crohn's disease cohort. These were pathology (all types) reports that contained only diagnosis information. No previous history, procedure type, gross, or other sections of the report was included.

Process

Step 1 – Identifying concepts by semantic type for each report

- We processed the Kennell reports through our text classification system using the UMLS ontology and identified 185,453 concepts.
- We filtered this set of concepts by semantic type to remove unrelated and uninteresting types.
- A report file was created containing the unique UMLS concepts by semantic type for validation
- An output file was created containing the Kennell report id, the UMLS concept, the semantic type and the matched term for each UMLS concept identified.

Step 2 – Applying Pittsburgh concepts to Kennell concepts

The Pittsburgh team had previously identified surgical pathology reports that were positive for Crohn's surgery (set A) and negative for Crohn's surgery (set B). Each pathology report set was processed through the same UMLS ontology used in Step 1 above for the Kennell set. The output contained positive and negative likelihood ratios for each UMLS concept /semantic type pair based on positive for surgery vs. negative for surgery.

- For each row in the output file from Step 1 above, we determined if this concept existed in the Pittsburgh positive group. If the concept existed AND the positive likelihood ratio was greater than 2.0, we wrote the Kennell report ID, concept, matched term and likelihood positive ratio to the results file.
- If the concept was found in the Kennell set and not in the Pittsburgh set, we did not write it to the results file.

There are 77 concepts that met both criteria - a positive likelihood ratio of >2.0 and found in the Pittsburgh positive group.

Step 3 – Result file findings

There were 1411 reports with at least 1 concept found in the Pittsburgh positive group. The highest number of concepts found in report was 23 and the lowest was 1. Some concepts may not be of interest (i.e. tip) individually but may be of interest when studied with other concepts found in the same report.

Example of output from Ontology Extraction program for University of Pittsburgh Pathology Reports

Concept Name	Matched Term	Negated?	Semantic Type	LR+	LR-
Ileal Stenosis	"ileum strictured"x1;"ileal strictur"x1;"ileum stricture"x11;"strictured ileum"x1;"Ileum strictures"x1;"ileum strictur"x2;"Ileal stricture"x1;"STRICTURE ILEUM"x2;"ILeum Stricture"x1;"ileal stricturing"x1;"stenosis ileum"x1;"ILEAL STRICTURE"x4;"ILEUM STRICTURE"x3;"stricture ileum"x1;"ileal stricture"x10;	N	Disease or Syndrome	6.4991	0.94908
Ileum wall	"ILEAL WALL"x1;"ileum wall"x9;"Ileum Wall"x1;"wall ileum"x7;"WALL ILEUM"x1;"ileal wall"x21;	N	Body Part, Organ, or Organ Component	6.3134	0.95080
Ileum with cecum	"ILEUM CAECUM"x2;"CECUM ILEUM"x1;"Ileum cecum"x6;"cecum ileum"x6;"ILEUM CECUM"x103;"ileum cecum""x1;"Ileum Cecum"x21;"ileum cecum"x114;"ileum Cecum"x1;"Cecum Ileum"x1;	N	Body Part, Organ, or Organ Component	4.8650	0.81417
Mucosal ulcer	"MUCOSAL ULCERATION"x47;"mucosal ulceration"x30;"ulceration mucosal"x1;"MUCOSAL ULCERATIONS"x3;"mucosal ulcerations"x8;"MUCOSAL ULCER"x1;"ulcerated mucosal"x5;"mucosal ulcer"x5;"MUCOSAL ULCERS"x6;"ULCERS MUCOSAL"x1;"ulcerations mucosal"x1;"mucosal ulcers"x20;"ULCERATION MUCOSAL"x1;"mucosal ulcerated"x1;"mucos ulcer"x2;"ulcer mucos"x1;	N	Acquired Abnormality	4.7350	0.85771
Ileal segment	"ileal segment""x1;"segment ileal"x2;"segmental ileal"x1;"ileal segment"x19;"ILEAL SEGMENT"x3;	N	Body Part, Organ, or Organ Component	4.0851	0.97143
Right hemicolectomy and end to end anastomosis of ileum to colon	"resection ileocecal"x3;"Ileocecal resection"x10;"Ileocecal Resection"x1;"ileocecal resection"x26;"ileocec resect"x10;"ILEOCECAL RESECTION"x13;	N	Therapeutic or Preventive Procedure	3.9923	0.94406
Colonic Fistula	"COLONIC FISTULA"x3;"colonic fistulae"x1;"colon fistula"x8;"COLON fistula"x1;"colonic fistula"x7;"Colonic fistula"x1;"COLON FISTULA"x11;"Colonic Fistula"x1;	N	Disease or Syndrome	3.8994	0.97315
Cecum mucosa	"mucosa cecum"x12;"CECAL MUCOSA"x3;"cecum mucosa"x7;"cecal mucosa"x49;"mucosa cecal"x2;	N	Body Part, Organ, or Organ Component	3.7756	0.92144
Ileitis	"NO ILEITIS"x1;"ILEITIS NO"x1;"ileitis" no"x1;"ileitis"x27;"ILEITIS"x152;"Ileitis"x1;	N	Disease or Syndrome	3.7403	0.81193
Stricture	"Stricture"x5;"STRICTURE"x176;"stricture"x485;"obstructing stricture"x1;	N	Anatomical Abnormality	3.6280	0.64411
Resection of cecum and ter	"TERMINAL ILEUM CECUM RESECTION"x18;	N	Therapeutic or Preventive Procedure	3.5281	0.97659
Ileocolic resection	"ILEOCOLIC RESECTION"x5;"ILeocolic Resection"x2;"Ileocolic Resection"x1;"ileocol resect"x5;"resection ileocolic"x2;"Resection ileocolic"x5;"ileocolic resection"x15;"Ileocolic resection"x9;	N	Therapeutic or Preventive Procedure	3.3424	0.95621
Fissure (external anatomical	"fissures"x21;"FISSURES"x8;"fissur"x3;"FISSURING"x32;"fissuring"x25;	N	Body Space or Junction	3.2495	0.91430
Length of segment	"length segmental"x4;"length segment"x56;	N	Finding	3.2186	0.93720

Concept Name	Matched Term	Negated?	Semantic Type	LR+	LR-
	"terminal ileum resection"x13;"terminal ileum resected"x2;"Resection terminal ileum"x4;"TERMINAL ILEUM RESECTION"x11;"Resection TERMINAL ILEUM"x1;"resection terminal ileum"x6;"Terminal ileum resection"x1;				
	"colon resected"x1;"Colon resection"x66;"COLON RESECTION"x66;"colon resect"x3;"COLONIC RESECTION"x41;"colonic resection"x48;"Colon Resection"x1;"Colon resections"x1;"colon resection"x46;"resection colonic"x1;"Resection colon"x2;"RESECTION COLON"x1;"colon resections"x1;"COLON resect"x2;"colonic' resection"x1;"Colonic resection"x3;"resection				
	"mucosa ileum"x4;"ileal mucosa"x79;"ileum		Body Part, Organ, or		
	"Ileocecectomy"x1;"ILEOCECECTOMY"x9;"ileocecectomy"x6;"ileocecectomi"x1;"ileo cecectomy"x2;"Ileocecectomy"x1;		Therapeutic or Preventive Procedure		
	"region ileocecal valve"x16;"region Ileocecal valve"x1;"REGION ILEOCECAL VALVE"x1;"ileocecal valve region"x4;		Body Location or		
	"ileocec"x3;"Ileocecal"x4;"ILEOCECITIS"x1;"ileocecal"x54;"ILEOCECAL"x8;				
	"COLON SEGMENTS RESECTION"x1;"segment resected colon"x1;"COLON SEGMENTAL RESECTION"x25;"COLON SEGMENT RESECTION"x1;"COLON SEGMENTAL RESECTIONS"x1;		Therapeutic or		
	"termin ileum"x71;"terminal ileum""x2;"ileum terminating"x1;"ileum termin"x1;"Terminal ileum"x19;"Terminal Ileum"x31;"Ileum Terminal"x1;"TERMINAL ILEUM"x237;"terminal Ileum"x1;"Terminal ILeum"x2;"ILEUM DISTAL PORTION"x1;"terminal ileum"x556;"distal portion ileum"x1;				
	"ileocec valv"x4;"ILEOCECAL VALVE"x34;"ileo cecal valve"x9;"ileocaecal valve"x1;"Ileocecal valve"x13;"ileocecal valve"x491;		Body Part, Organ, or		
	"Ileocolic anastomosis"x2;"ILEUM COLON ANASTOMOSIS"x1;"ileocolic anastomosis"x4;"ILEOCOLIC ANASTOMOSIS"x16;"ileocol anastomosi"x6;"Ileocolic Anastomosis"x2;"COLON				
	"ileocolectomy"x15;"ILEOCOLECTOMY"x23;"ileocol		Therapeutic or Preventive Procedure		
	"ileectomy"x1;"ILEECTOMY"x1;"ILEUM RESECTION"x13;"ILEAL RESECTION"x24;"resection ileum"x5;"ileal resected"x1;"ileal resect"x1;"resection ileal"x2;"Resection ILEUM"x2;"ILEUM EXCISION"x6;"ileal resection"x48;"resected ileum"x2;"ILEUM resect"x1;"Ileal resection"x2;"Resection ileum"x1;				

Concept Name	Matched Term	Negated?	Semantic Type	LR+	LR-
	"LYMPH NODES PERICOLONIC"x1;"lymph nodes pericolonic"x3;"pericolonic lymph nodes"x7;"pericolonic lymph node"x1;"PERICOLONIC LYMPH NODES"x14;				

Example of output from Ontology Extraction program for Military Health System Pathology Reports

report	concept_name	matched_term	semantic_type	LR+
9	distal part of ileum	terminal ileum	Body Part, Organ, or Organ Componer	2.412
9	Terminal	terminal	Temporal Concept	2.334
10	distal part of ileum	terminal ileum	Body Part, Organ, or Organ Componer	2.412
10	Terminal	terminal	Temporal Concept	2.334
11	Fibrous obliteration	fibrous obliteration	Pathologic Function	4.059
12	distal part of ileum	terminal ileum	Body Part, Organ, or Organ Componer	2.412
12	Terminal	terminal	Temporal Concept	2.334
12	Enteritides	enteric	Disease or Syndrome	5.073
13	Massive	marked	Qualitative Concept	2.345
13	distal part of ileum	terminal ileum	Body Part, Organ, or Organ Componer	2.412
13	Terminal	terminal	Temporal Concept	2.334
16	Abnormal	abnormalities	Qualitative Concept	2.131
17	distal part of ileum	terminal ileum	Body Part, Organ, or Organ Componer	2.412
17	Terminal	terminal	Temporal Concept	2.334
17	Ileum and colon, CS	ileum colonic	Body Location or Region	2.870
17	Ileal mucous membrane	ileum mucosa	Body Part, Organ, or Organ Componer	4.018
17	Massive	marked	Qualitative Concept	2.345
19	distal part of ileum	terminal ileum	Body Part, Organ, or Organ Componer	2.412
19	Terminal	terminal	Temporal Concept	2.334
19	ulcerated	ulceration	Finding	2.041
20	Chronic active	chronic active	Functional Concept	2.041
21	distal part of ileum	terminal ileum	Body Part, Organ, or Organ Componer	2.412
21	Terminal	terminal	Temporal Concept	2.334
21	Ileal mucous membrane	ileal mucosa	Body Part, Organ, or Organ Componer	4.018

Appendix 4 – Results for AP Cohort and Prediction of ICU Admission, Death, and Organ Failure

Table 1 – Number of SIRS criteria fulfilled

Score	Day 1	Day 2-5
0	260	131
1	466	359
2	242	178
3	66	79
4	10	31

Table 2 – ICU Admission by SIRS

	ICU admission of duration ≥ 48 hours within first 7 days of admission	
	No	**yes**
SIRS < 2	658	68
SIRS ≥2	256	62

Table 3- Persistent organ failure by SIRS

	Persistent organ failure	
	No	**yes**
SIRS < 2	621	105
SIRS ≥2	232	86

Table 4 – Death within 90 days by SIRS

	Death within 90 days of admission	
	No	**yes**
SIRS < 2	722	4
SIRS ≥2	307	11

Table 5 – Death within 90 days of admission by ICU Stay

	Death within 90 days of admission	
ICU stay ≥48 hours	**No**	**Yes**
No	906	8
Yes	123	7

Table 6: Prevalence of ICU admission, persistent OF and death (within 90 days of admission) based on presence of SIRS. Numbers are counts (percent).

	N	**Risk N - (%)**		
		ICU admission (≥48 hrs)	**Persistent OF**	**Death**
SIRS (Day 1)				
<2	726	68 (9.3%)	105 (14.4%)	4 (0.6%)
≥2	318	62 (19.5%)	86 (27.0%)	11 (3.4%)
ICU admission				

None or <48 hours	914	-	-	8 (0.9%)
≥48 hours	130	-	-	7 (5.4%)

Table 7: Predictive value of SIRS and ICU admission for outcomes of interest (multivariate logistic regression). Adjusted for age (in years), gender, race, Charlson score, and etiology

Dependent variable	Outcome	OR (95% CI)	p-value
Admission SIRS ≥2	ICU ≥48 hours	3.6 (2.2, 5.7)	<0.0001
	Persistent OF	4.2 (2.8, 6.9)	<0.0001
	Death	5.1 (1.4, 9.3)	<0.0001
ICU stay ≥48 hours	Death	6.6 (2.2, 9.6)	0.001

Table 8. Timing of SIRS in relation to persistent OF, ICU stay ≥48 hours, and death (within 90 days of admission). Numbers are counts.

	SIRS start time		
Markers of severity	**Day 1 (SIRS ≥2) n = 318**	**Day 2-5 (SIRS ≥2 and SIRS < 2 on day 1) n = 74**	**No SIRS (SIRS < 2) n = 330**
Persistent OF	86	23	82
ICU stay ≥48 hours	62	21	47
Death	11	2	2

Table 9. Duration of SIRS in relation to persistent OF, ICU stay ≥48 hours, and death (within 90 days of admission). Numbers are counts. P value is obtained from 2-sided Fisher's exact test.

	Duration of SIRS			
Markers of severity	**No SIRS n = 330**	**Transient SIRS (≤ 48 hours) n = 210**	**Persistent SIRS (> 48 hours) n = 118**	**P value**
Persistent OF	82	34	40	0.001
ICU stay ≥48 hours	47	21	32	<0.0001
Death	2	4	9	<0.0001

Table 10. Risk of developing persistent SIRS for patients with SIRS on Day 1 (A) and patients with 3 or 4 SIRS criteria on Day 1 (B). Numbers are counts (percent). OR [95% C.I.] and P value are obtained from 2-sided chi square test.

A	**SIRS day 1 (n = 318)**	**SIRS after day 1 (n = 74)**	**OR (95% CI)**	**P value**
Persistent SIRS	108 (33.9%)	10 (13.5%)	3.3 (1.6, 6.7)	0.0006
B	**SIRS = 3 or 4 criteria day 1 (n = 70)**	**SIRS < 3 criteria day 1 (n = 974)**	**OR (95% CI)**	**P value**
Persistent SIRS	32 (45.7%)	86 (8.8%)	8.7 (5.2, 14.6)	<0.0001

Appendix 5 – Manuscript describing GIANT and Concept Extraction

Automated Identification of a Complex Phenotype from Electronic Health Records

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Keywords: EHR-derived phenotyping, annotation, machine learning, classification, Crohn's disease

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ABSTRACT

Objective

Electronic health records (EHR) offer the promise of rapid identification of patient cohorts to support translational research. While current query tools based on easily searchable diagnostic and laboratory codes can identify broad phenotypic categories, they lack the capability for accurate automated identification of specific outcomes and complications that comprise the complex disease phenotypes needed for advanced clinical research. We developed an annotation tool and classification models to identify an important complex phenotype, severe Crohn's disease (CD) with complications requiring bowel surgery.

Design

We developed an annotation tool to provide both automatic concept identification and manual annotation of free text clinical reports. The tool was applied to 1,517 operative reports of patients with CD. Classification models were developed using naive Bayes, logistic regression and support vector machine (SVM). The models were trained with ICD-9 codes alone, UMLS concepts alone, and both ICD-9 codes and UMLS concepts to identify reports with CD-related surgery. We compared the performance of the classification models using 20-fold cross-validation.

Results

Classification models trained with UMLS concepts alone had statistically significantly better AUCs and accuracies than models trained with ICD-9 codes alone. Moreover, using both ICD-9 codes and UMLS concepts did not improve performance over using UMLS concepts alone. The best performance was obtained with a SVM model that had an AUC of 0.912 with a 95% confidence interval of (0.883 - 0.943). In comparison, a SVM model trained with ICD-9 codes had an AUC of 0.618 (0.583 - 0.642).

Discussion and Conclusion

The annotation tool was easy to use for manual annotations and automatically extracted UMLS concepts with excellent performance. The combination of manual and automatic annotations in conjunction with a classification model allows accurate identification of cohorts with complex phenotypes.

I. INTRODUCTION

Healthcare systems are rapidly adopting electronic health record (EHR) systems for clinical documentation, coding and billing, driven by the primary goals of improving healthcare quality, increasing patient safety and decreasing costs. The broad adoption of EHRs has brought the added promise of reuse of healthcare data to enable research studies ranging from clinical trials to translational science. However, current EHRs largely lack the needed functionality to support translational research, such as de-identified data sharing, extraction of biomedical concepts, and the phenotyping of complex diseases and outcomes. There is a great need to develop the software tools and computational methods to extract and manipulate data in EHRs to enable research [1].

Identification of patient cohorts is a key component of clinical, genomic, translational and comparative effectiveness research; this task is typically expensive in effort and in time. EHRs with their large stores of clinical data from patient encounters offer the promise of rapid identification of patient cohorts using computational algorithms and methods to select and retrieve sets of patients. Efficient and accurate identification of appropriate patient cohorts requires tools that can perform EHR-derived phenotyping in a high-throughput manner. Simple logical queries can be applied to structured data such as International Classification of Diseases (ICD-9) codes and standardized laboratory test codes to identify patients with certain characteristics. However, a significant amount of clinical information is present only in free-text clinical reports such as discharge summaries and operative reports. Free-text descriptions of the outcomes and disease complications that are important for defining complex clinical phenotypes cannot be accurately captured using current EHR query tools.

Natural language processing (NLP) methods can now extract much useful information such as defined medical concepts from free-text clinical reports, and their precision continues to improve. In addition, machine learning methods can be applied to identify clinical documents of interest. Ongoing research has shown that NLP and machine learning methods can be applied successfully to EHR data for identifying the presence of a disease such as rheumatoid arthritis [2]. However, much less work has been done in identifying complications, outcomes or subphenotypes automatically from EHR data. Typically they cannot be readily or accurately identified by simple automated methods based on ICD-9 codes or other coded medical concepts. For example, in an ongoing research project a key task is identifying a cohort of patients with severe Crohn's disease (CD), defined by the need for intestinal resection, stricture repair, fistula takedown or intestinal transplantation. Identifying if a patient had a surgical procedure performed for one of these specific complications of CD in an operative report is not straightforward and has required a domain expert to interpret each text report.

To address EHR-derived phenotyping of such complex phenotypes we developed a software tool called the GI Annotation Tool (GIANT) that enables both automatic identification of concepts in free text clinical reports and manual annotation by clinicians. The concepts and annotations that are output from GIANT allow the development of machine learning models to predict if the complex phenotype was present in a report.

In this paper we describe the components of GIANT and its application both to automatically identify UMLS concepts and to manually annotate CD-related surgical events in 1,517 free text operative reports. For comparison, we also obtained ICD-9 codes associated with the operative reports. We compared the performance of classification models trained with UMLS concepts to determine if it could deliver superior performance in identifying CD-related surgical events compared with that models trained with the more easily obtainable ICD-9 codes. A positive result would support using UMLS concepts for identifying complex phenotypes such as severe CD in a semi-automated fashion from EHR data.

II. BACKGROUND

In this section we briefly describe EHR-driven phenotyping, Crohn's disease, and the Medical Archival System (MARS) at the University of Pittsburgh Medical Center (UPMC).

EHR-derived Phenotyping

EHRs contain easily searchable structured data such as demographics, laboratory values, medication orders, physiological measurements, and coded diagnoses. Even more data are available in unstructured free text formats as admission and discharge notes, progress notes, imaging and pathology reports and operative notes. In some institutions these data are extracted and available in research data marts; examples include the Partners data mart that uses the integrating biology and the bedside (i2b2) technology [3], the Vanderbilt Synthetic Derivative [4], and the Medical Archival System (MARS) at the University of Pittsburgh [5].

With increasing penetration of EHRs it is becoming possible to quickly construct large cohorts of patients of a phenotype of interest. Typically, a cohort is constructed by querying a data mart using a phenotyping algorithm developed for the phenotype of interest. Algorithms may consider only structured data or a combination of structured and free text data [6].

Because EHR-derived phenotyping algorithms that use ICD-9 coded diagnoses from billing data have limited accuracy [7-9], recently NLP tools have been applied to free text reports to extract phenotype information. Typically, these tools identify medical terms and phrases in free text and map them to controlled vocabularies

defining medical concepts, such as the unified medical language system (UMLS). Examples of such tools include the clinical Text and Knowledge Extraction System (cTAKES) [10], the Health Information Text Extraction (HITEx) system [11] and Ontology development and information extraction (ODIE) toolset [12]. Friedlin et al found that an NLP method had better performance than an ICD-9-based method in identifying pancreatic cancer patients [13]. Furthermore, we and others have applied machine learning methods to free text clinical reports to identify complex phenotypes such as complications and adverse drug events [14, 15].

Researchers have developed several tools for manual or semi-automated annotation of free text clinical documents. For example, South et al. annotated several hundred clinical documents of patients with inflammatory bowel disease using Protégé and the Knowtator tool [16]. Song et al. developed a semi-automatic tool called Semantator that can be used for document annotation with Semantic Web ontologies. Such tools are also useful in annotating and extracting complex phenotypes from EHR data [17].

The Medical Archival System (MARS)

MARS is a repository for information forwarded from UPMC's electronic clinical, administrative, and financial databases. MARS receives daily feeds from the EHRs in UPMC's 20 hospitals. It currently houses over 400 million clinical documents and 800 million financial transactions.

The MARS architecture and implementation of the repository have evolved to take advantage of storage area network systems and distributed, parallel processors in a virtualized workstation environment making it amenable for storing large amounts of textual data. MARS is indexed on every word and every number for efficient retrieval.

Records in the MARS repository are stored as a set of code-value pairs. There are approximately 100 codes supported to represent records in the database. Fields are defined for common data such as patient name and medical record number while other fields are specific to particular record types, such as the body of a radiology report or a progress note. The suite of available codes effectively constitutes a flat table definition. For each record, only fields that are populated are stored in the database. When records are inserted into the database each word in each field is indexed.

While the MARS architecture is superior for storing, indexing and retrieving of clinical reports, it remains difficult to identify and capture discrete data elements. Searching is also limited to specific words and the system does not support stemming or other advanced searching techniques.

Crohn's Disease

Crohn's disease is an incurable, complex, life-long disorder that affects over 600,000 Americans at a cost of $2 billion per year [18-21]. Most patients are diagnosed before age 40, within their peak period of work productivity and military service. About one third of CD patients experiences few or no significant disease manifestations over their lifetime and requires minimal therapy to enjoy full quality of life. In contrast, however, one quarter of CD patients have a severe phenotype that leads to multiple surgical procedures, disability, intestinal failure, and risk of premature death; these patients are the most likely to benefit from early biologic therapy (e.g., anti-tumor necrosis factor-alpha antibody treatment). Thus, predicting severity at the time of diagnosis is a critical unmet need for the efficacious treatment of CD.

III. SYSTEM DESCRIPTION

In this section we describe the GI Annotation Tool and its components.

GIANT is web-accessible annotation tool that allows two types of annotations including 1) automatic identification of medical concepts such as those defined in the UMLS, and 2) manual annotation for determining complex phenotypes and outcome assessment. Given a set of documents, GIANT can output both automated and manual annotations for further analyses. Figure 1 shows the two components of GIANT including the Annotation Module for manual annotation and the Concept Extraction Module for automatic concept annotation and extraction. As shown in the figure, GIANT receives clinical documents from MARS and sends manual and automatic annotations to a clinical research database that is an instance of i2b2. i2b2 is a software suite to construct a clinical research database from EHR data and to integrate genomic and other types of research data [3].

GIANT uses a MySQL database and its interface is built using the Django (www.djangoproject.com) web framework, which is written in the Python programming language. Django has several features that streamline the software development process and allow rapid development of functionality such as interactions with the database and navigation of reports in the web interface.

GIANT contains a user authentication system that handles all the tasks necessary to create, maintain and delete user accounts. An administrative interface offers basic create, read, update, and delete functionality for database maintenance. Documents in GIANT are organized in projects and typically each project is associated with a set of users who will manually annotate the documents. Each project is also associated with a set of variables and possible values that are displayed in a web form to enable rapid manual annotation that is relevant

to the project. Figure 2 shows a screenshot of the manual annotation interface that contains an example document and an annotation form with a set of variables.

In addition to manual annotation, GIANT uses the Ontology Development and Information Extraction (ODIE) toolset for automatic annotation (see Figure 3). ODIE can use any controlled vocabulary or an ontology such as the UMLS and will identify the ontological concepts in free text documents.

GIANT is currently deployed and has over twenty active or completed projects. Hospital and university information technology security teams ensured that GIANT meets institutional security policies. GIANT contains only de-identified data and is accessible from only the hospital and university networks.

Typically there are two types of output from GIANT. The first type of output is document annotations that have been completed by clinical domain experts and the second type consists of UMLS (the most commonly used terminology in GIANT) concepts that have been automatically by ODIE; both outputs are imported into the clinical research database. The manual and automatic annotations can be retrieved from the clinical research database for further analyses such as for developing classification models as described in the next section.

IV. METHODS

Patient cohort

Patients with CD who had been hospitalized from January 1, 1995 to June 30, 2007 at UPMC's Presbyterian campus (the primary site of most major surgeries in UPMC) were identified from inpatient discharge abstracts by using a primary or secondary ICD-9 diagnosis code of 555.1–555.9. Among this group of CD patients, patients who had undergone bowel surgery were identified by using the following ICD-9 procedure codes: 45.33, 45.51, 45.61, 45.62, 45.63, 45.72, 45.73 45.90, 45.91, 45.92, 45.93, 46.01, 46.20, 46.21, 46.22, 46.23, 46.40, 46.41, 46.51, 46.73, 46.74, 46.79, 46.81, 46.93, 46.99, 57.83, 57.84. Operative reports of these patients were obtained from MARS and were de-identified using De-Id by an honest broker. De-Id is a de-identification software for clinical free text reports that was developed at University of Pittsburgh and is commercially available from De-Id Data Corp., Richboro, PA [22] .

Annotation and concept extraction with GIANT

GIANT was used for both manual annotation and automatic UMLS concept annotation in the operative reports. Two authors (JMS, MR) who are experts in CD developed the annotation form for determining CD related

surgical complications based on the criteria adopted by the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK) Inflammatory Bowel Disease Genetics Consortium (IBDGC). A screenshot of the form as implemented in GIANT is shown in Figure 4. The reports were evaluated using the Annotation Module by a CD expert (JMS) and were labeled either as CD-related surgery or non-CD-related surgery. The first fifty reports were evaluated by two CD experts (JMS, MR) to ensure agreement. CD-related surgery was defined by the need for intestinal resection, stricture repair, fistula takedown or intestinal transplantation in patients who had a diagnosis of CD.

For each report, UMLS concepts were annotated automatically using the Concept Extraction Module with UMLS (UMLS version 2012AB, November 15, 2012). In addition, associated ICD-9 codes were obtained separately from MARS.

Classification models

To evaluate the utility of the ICD-9 codes and the UMLS concepts in their ability to predict if an operative report documented CD-related surgery, we constructed classification models using i) ICD-9 codes alone to predict if a report is CD-related surgery or non-CD-related surgery, ii) UMLS concepts alone to predict if a report is CD-related surgery or non-CD-related surgery, and iii) both ICD-9 codes and UMLS concepts to predict if a report is CD-related surgery or non-CD-related surgery. We applied three machine learning methods to train the classification models, including naïve Bayes (NB), logistic regression (LR) and Support Vector Machine (SVM).

The NB method derives a probabilistic model that makes the assumption that features (ICD-9 codes or UMLS concepts) of a report case are conditionally independent of each other given its label [23]. The parameters for the NB model include the probabilities for the report label and conditional probabilities for the features being considered. These are computed as follows. Let Y represent a report and y denote the two possible values that it can take -- CD-related surgery or non-CD-related surgery. Let X_i represent a feature and x denote the two possible values that it can take -- present or absent. Suppose $\boldsymbol{X}$ is a set of n features, each of which is known to be either present or absent. The probability of y given $\boldsymbol{X}$ is computed according to Bayes' rule:

$$P(Y = y|X) = \frac{P(Y = y)\prod_{i=1}^{n} P(X_i = x|Y = y)}{\sum_Y\{P(Y)\prod_{i=1}^{n} P(X_i = x|Y = y)\}}$$

where n is the number of features in the model and the sum in the denominator is over all possible values of Y. We estimate the probabilities $P(Y = y)$ and $P(X_i = x \mid Y = y)$ for the four possible combination values of x and y. $P(Y = y)$ is estimated as $(freq(Y = y) + 1) / (N + 2)$ where $freq(Y = y)$ is the number of reports with label y and N is the total number of reports in the training set. Similarly, $P(X_i = x \mid Y = y)$ is estimated as $(freq(X_i = x, Y = y) + 1) / (freq(Y = y) + 2)$ where $freq(X_i = x, Y = y)$ is the number of times that x and y occur together in the training set. These ratios produce estimates that are less extreme than maximum likelihood estimates based on the ratios $freq(X_i = x, Y = y) / freq(Y = y)$ and $freq(Y = y) / N$ and are typically associated with better classifier performance [24].

Logistic regression derives a parametric classification model that learns a function of the form $P(Y|\boldsymbol{X})$, where Y denotes the report, and $\boldsymbol{X}$ is a set of n features, each of which is known to be either present or absent. To improve the estimation of parameters of the LR model, we chose the ridge estimator [25].

The SVM method derives a non-probabilistic linear classification model that represents a hyperplane in the feature space that separates CD-related surgery reports from non-CD-related surgery reports [26].

Evaluation

The performance of the classification models was evaluated using 20-fold cross-validation to avoid bias. The dataset was randomly partitioned into 20 approximately equal sets such that each set had a similar proportion of CD-related surgery and non-CD-related surgery reports. As an example, for the experiment that used UMLS concepts as features and NB as the classification method, we trained a NB model on 19 sets and evaluated it on the remaining test set, and we repeated this process once for each possible test set. We thus obtained a prediction (CD-related surgery or non-CD-related surgery) for each of the 1,517 reports.

The performance measures included the area under the receiver operating characteristic curve (AUC) and accuracy. Their estimates with 95% confidence intervals were calculated using the average obtained from each fold of the cross-validation.

IV. RESULTS

A total of 1,517 operative reports were obtained from MARS that met the criteria of having CD and bowel surgery. Of the 1,517 reports, 879 were labeled as CD-related surgery and 638 as non-CD-related surgery. A total of 1,704 distinct UMLS concepts were identified in the reports and a total of 42 distinct operative ICD-9 codes were associated with the reports.

Table 1 reports the AUCs and Table 2 reports the accuracies obtained from the three classification methods. Across all three classification methods, models that were trained with UMLS concepts alone performed statistically significantly better on both AUC and accuracy than models that were trained with ICD-9 codes alone. Moreover, models that were trained with both ICD-9 codes and UMLS concepts did not perform better than the models that were trained with UMLS concepts alone. The LR and SVM models performed slightly better than the NB models but the difference in performance was not statistically significant.

Table 1. AUCs of classification models trained with ICD-9 codes alone, UMLS concepts alone, and both ICD-9 codes and UMLS concepts in identifying CD-related surgical events in operative reports.

Classification method	ICD-9 codes (95% CI)	UMLS concepts (95% CI)	ICD-9 codes and UMLS concepts (95% CI)
NB	0.587 (0.556 - 0.605)	0.891 (0.872 - 0.923)	0.872 (0.853 - 0.901)
LR	0.612 (0.582 - 0.638)	0.901 (0.881 - 0.936)	0.899 (0.878 - 0.924)
SVM	0.618 (0.583 - 0.642)	0.912 (0.883 - 0.943)	0.911 (0.872 - 0.923)

Table 2. Accuracies of classification models trained with ICD-9 codes alone, UMLS concepts alone, and both ICD-9 codes and UMLS concepts in identifying CD-related surgical events in operative reports.

Classification method	ICD-9 codes (95% CI)	UMLS concepts (95% CI)	ICD-9 codes and UMLS concepts (95% CI)
NB	68.4% (66.2% - 70.1%)	80.4% (78.3% - 82.6%)	80.4% (78.3% - 82.6%)
LR	71.2% (68.1% - 73.2%)	82.1% (79.8% - 83.9%)	82.5% (79.5% - 83.8%)
SVM	72.3% (69.8% - 74.4%)	83.5% (80.2% - 85.3%)	83.2% (80.1% - 85.7%)

V. DISCUSSION

Rapid EHR-derived phenotyping is a promising approach for identifying patient cohorts for clinical, translational and genomic research. Phenotyping methods that employ machine learning methods operating on a range of structured and unstructured EHR data have been developed and shown to have good performance [27] as well as shown to be portable across institutions [15]. Most of these methods are defined for identifying broad disease phenotypes such as rheumatoid arthritis, peripheral artery disease or CD.

However, in addition to identifying broad disease phenotypes, translational and clinical research often requires identifying patient cohorts with complex subphenotypes that may be defined by disease related

complications or outcomes such as severe CD requiring bowel surgery. Broad disease phenotypes such as CD can be reliably identified automatically from structured data such as ICD-9 codes and medications [28] though sometimes their identification may also require both structured data and concepts that are extracted from free text clinical documents [15]. Identification of complex subphenotypes is more likely to require the parsing of clinical free text documents. Our results show that a specific severe CD phenotype such as disease requiring bowel surgery is not readily identifiable by ICD-9 codes alone. In general for translational research, recognition of complex disease phenotypes where ICD-9 codes and other types of structured data such as medications and laboratory test results are of limited precision and value is central for identifying complications or outcomes related to that disease. In such situations, using features extracted automatically along with expert annotation of a complex phenotype of interest can be used to train classification models that can be applied to a large set of clinical documents to reliably identify patients in whom the phenotype is present. In our study classification models trained with UMLS concepts achieved high efficiency and superior performance in identifying CD-related surgical events in operative reports.

Limitations

This study has several limitations. We evaluated only one type of clinical report and one complex phenotype in one disease. Other clinical reports and complex phenotypes in other diseases may have different performances. Another limitation is that we did not evaluate calibration of the models. A model is well calibrated if the probability predicted for a label corresponds closely to the empirical frequency of that label [29]. Well calibrated models are essential for applying decision analytical methods for selecting the appropriate probability threshold above which an event will be labeled as CD-related surgery.

Future considerations

Future development of GIANT is planned to investigate the generalizability and portability of this tool for complex phenotyping from the EHR. Further development will include integration of the classification methods as modules so that a user of GIANT will be able use its manual and automatic annotations to learn and apply classification models. For example, in an enhanced GIANT tool, a user might label only a fraction of the reports, learn a classification model from the labeled fraction of reports and apply the model to the remaining reports to label them automatically. In addition, integration of GIANT with freely available clinical research informatics tools, such as i2b2, will enable its widespread use beyond a single institution.

Further evaluation of GIANT for generalizability is needed for other types of clinical documents such as radiology reports, consultation notes and discharge summaries, as well as for the wide variety of complex phenotypes that are derived from real clinical research studies. Finally, study is needed to evaluate the portability of GIANT to other institutions with similar and different EHR systems.

VI. CONCLUSION

We developed a software tool for identifying complex phenotypes from free text EHR reports using a combination of manual and automatic annotations. We used the tool to annotate a set of operative reports in patients with CD. Classification models trained with UMLS concepts achieved superior performance in identifying CD-related surgical events compared with that of models trained with ICD-9 codes. This work suggests that complex phenotype identification can be achieved with a judicious mix of manual and automatic methods combined with classification models. Future work should integrate the classification models with the annotation tool and evaluate it on additional complex phenotypes.

Acknowledgements

We thank Richard Wilson and Greg Gardner for their work on the prototype database for GIANT.

Funding

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Figure Legends

Figure 1. System overview showing the two components of GIANT including the Annotation Module this is used for manual annotation and the Concept Extraction Module that is used for automatic concept annotation. MARS is a EHR-data repository, and De-Id is a de-identification software available from De-Id Data Corp., Richboro, PA.

Figure 2. Screenshot of the Annotation Module in GIANT showing a portion of a de-identified operative report on the left and an annotation form on the right.

Figure 3. Screenshot of the Concept Extraction Module in GIANT showing UMLS concepts that have been identified a de-identified operative report.

Figure 4. Screenshot of the annotation form that was used for annotating operative reports for CD-related operative events.

Figure 1.

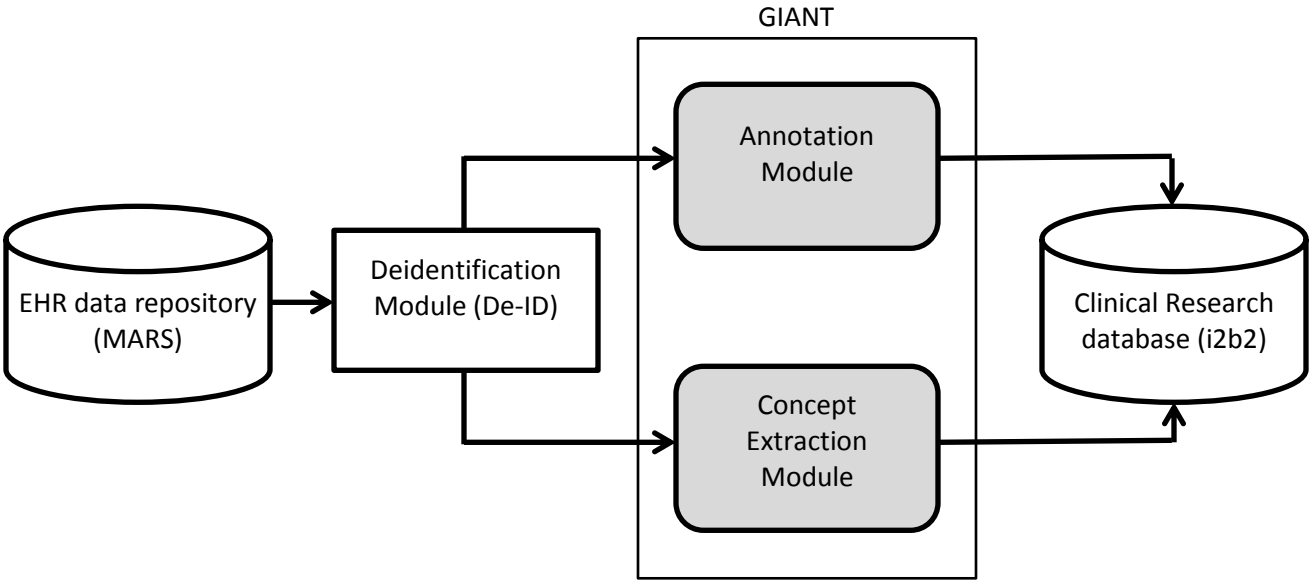

GIANT
Annotation Module
EHR data repository (MARS)
Deidentification Module (De-ID)
Concept Extraction Module
Clinical Research database (i2b2)

Figure 2.

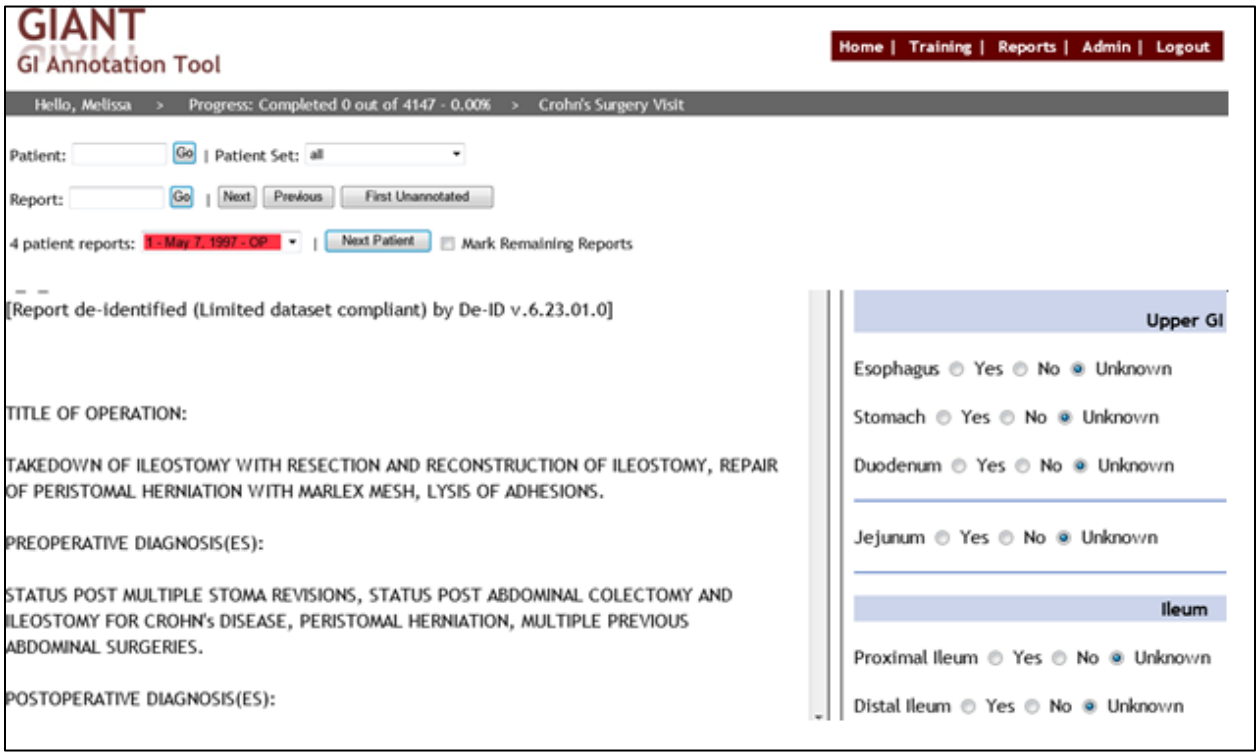
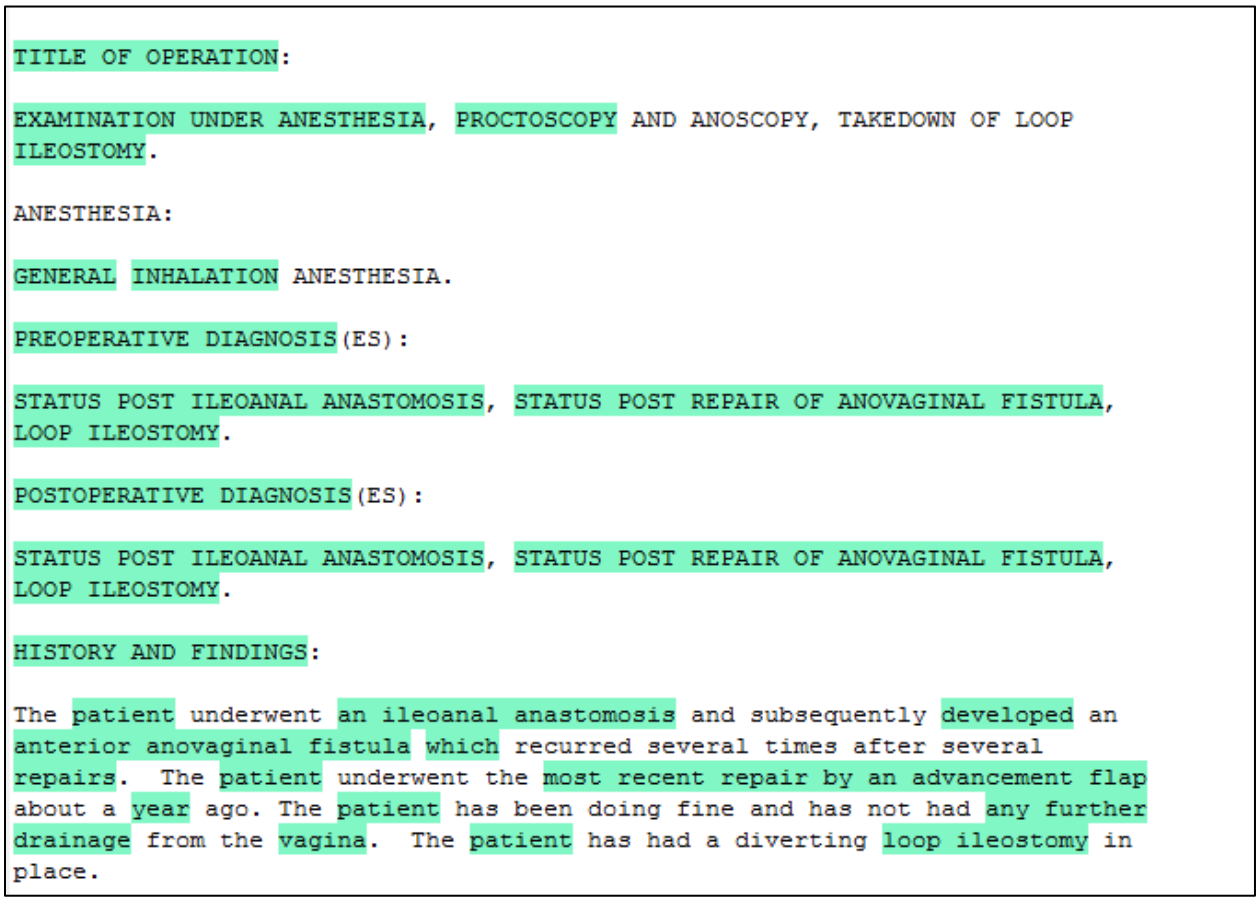

GIANT
GI Annotation Tool
Home | Training | Reports | Admin | Logout
Hello, Melissa > Progress: Completed 0 out of 4147 - 0.00% > Crohn's Surgery Visit
Patient: Go | Patient Set: all
Report: Go | Next Previous First Unannotated
4 patient reports: 1 - May 7, 1997 - OP | Next Patient Mark Remaining Reports
[Report de-identified (Limited dataset compliant) by De-ID v.6.23.01.0]
TITLE OF OPERATION:
TAKEDOWN OF ILEOSTOMY WITH RESECTION AND RECONSTRUCTION OF ILEOSTOMY, REPAIR OF PERISTOMAL HERNIATION WITH MARLEX MESH, LYSIS OF ADHESIONS.
PREOPERATIVE DIAGNOSIS(ES):
STATUS POST MULTIPLE STOMA REVISIONS, STATUS POST ABDOMINAL COLECTOMY AND ILEOSTOMY FOR CROHN's DISEASE, PERISTOMAL HERNIATION, MULTIPLE PREVIOUS ABDOMINAL SURGERIES.
POSTOPERATIVE DIAGNOSIS(ES):
Upper GI
Esophagus Yes No Unknown
Stomach Yes No Unknown
Duodenum Yes No Unknown
Jejunum Yes No Unknown
Ileum
Proximal Ileum Yes No Unknown
Distal Ileum Yes No Unknown

Figure 3.



TITLE OF OPERATION:

EXAMINATION UNDER ANESTHESIA, PROCTOSCOPY AND ANOSCOPY, TAKEDOWN OF LOOP ILEOSTOMY.

ANESTHESIA:

GENERAL INHALATION ANESTHESIA.

PREOPERATIVE DIAGNOSIS(ES):

STATUS POST ILEOANAL ANASTOMOSIS, STATUS POST REPAIR OF ANOVAGINAL FISTULA, LOOP ILEOSTOMY.

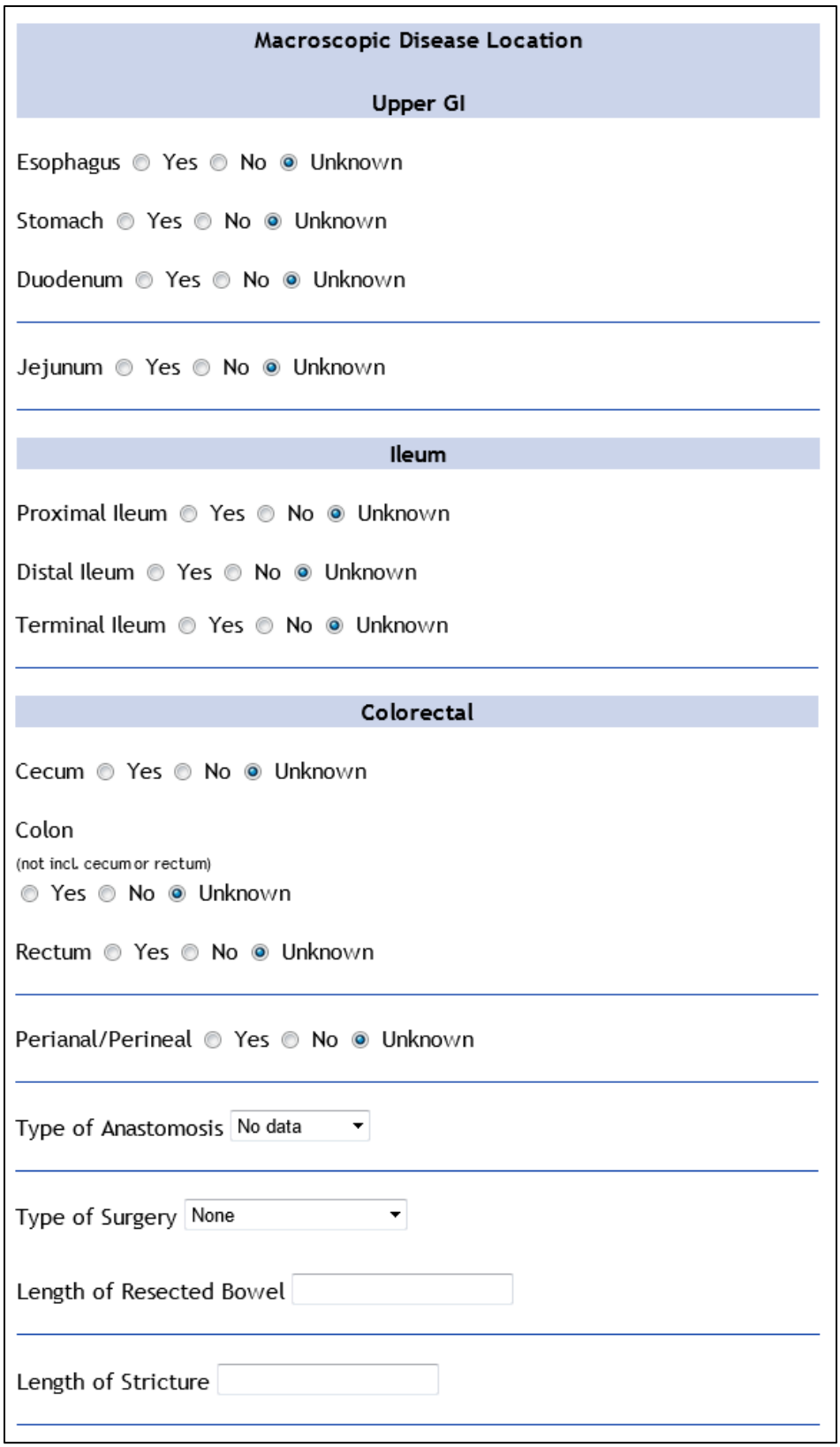
POSTOPERATIVE DIAGNOSIS(ES):

STATUS POST ILEOANAL ANASTOMOSIS, STATUS POST REPAIR OF ANOVAGINAL FISTULA, LOOP ILEOSTOMY.

HISTORY AND FINDINGS:

The patient underwent an ileoanal anastomosis and subsequently developed an anterior anovaginal fistula which recurred several times after several repairs. The patient underwent the most recent repair by an advancement flap about a year ago. The patient has been doing fine and has not had any further drainage from the vagina. The patient has had a diverting loop ileostomy in place.

Figure 4.


Macroscopic Disease Location
Upper GI
Esophagus Yes No Unknown
Stomach Yes No Unknown
Duodenum Yes No Unknown
Jejunum Yes No Unknown
Ileum
Proximal Ileum Yes No Unknown
Distal Ileum Yes No Unknown
Terminal Ileum Yes No Unknown
Colorectal
Cecum Yes No Unknown
Colon
(not incl. cecum or rectum)
Yes No Unknown
Rectum Yes No Unknown
Perianal/Perineal Yes No Unknown
Type of Anastomosis No data
Type of Surgery None
Length of Resected Bowel
Length of Stricture

Appendix 6 – Abstracts Presented at National Meetings

1. Current Spectrum of Liver Disease in Inflammatory Bowel Disease

Michael A. Dunn[1], Claudia M. Ramos Rivers[1], Amy R. Schmotzer[1], Miguel D. Regueiro[1], Kapil B. Chopra[1], David G. Binion[1]
Medicine, University of Pittsburgh, Pittsburgh, PA, United States.

Introduction: Liver disease is an established extraintestinal comorbidity associated with inflammatory bowel disease (IBD; Crohn's disease (CD), ulcerative colitis (UC)). Historically, primary sclerosing cholangitis (PSC) was associated with UC and this biliary lesion was the dominant form of hepatic injury. Currently it is unknown whether the rising percentage of patients with CD and changing demographics of the US population including the rise in obesity have impacted IBD and patterns of associated liver disease. We evaluated a prospective IBD patient registry to characterize the patterns of liver disease in IBD at the present time.
Methods: A prospective IBD patient registry between 2009–2011 was queried. All patients with chronic liver disease indicated on ICD-9 coding were identified, as were patients who had undergone liver biopsy and CT or MR imaging demonstrating hepatic pathology.
Results: There were 1463 IBD patients evaluated (UC 590 and CD 873) and 6% (n=89) had liver disease. Among the 590 UC patients 5.7% were identified as having PSC (n=34) and 1% (n=6) were found to have nonalcoholic steatohepatitis (NASH). Overall liver disease was identified in 8.8% of the UC patients (n=52).
The body mass index (BMI) of the PSC patients was 26.3 + 5.0. The 6 patients with NASH had a BMI of 32.7 + 4.2. Seven of 34 PSC patients (20.6%) required transplants, as did 2 others (one for Budd Chiari syndrome and one for autoimmune hepatitis with cirrhosis). No NASH patient required a transplant. BMI in the 590 UC patients was 28.3 + 6.1, and 205 of 590 (34.7%) were obese with BMI 30 or above.
Among the 873 CD patients, 2.2% had PSC (n=20) and 1% had NASH (n=9). 4.3% of CD patients had coding for any concomitant liver disease (n=37). The 20 CD PSC patients had a BMI of 24.1 + 4.0, while the 9 CD NASH patients had a BMI of 31.5 + 7.8. Two of 20 CD PSC patients (10%) required transplants while 1 out of the 9 CD NASH patients required a transplant. BMI in the 873 CD patients was 27.5 + 6.1 and 251 of 873 (28.7%) were obese with BMI of 30 or above.
There were no differences in utilization pattern of 12 specific IBD medications (4 biologics, 3 immunomodulators, 4 aminosalicylates, and prednisone) between UC and CD patients with PSC or NASH compared with those without liver disease.
Conclusion: Liver disease occurs in a minority of IBD patients, with PSC making the biggest contribution in both UC and CD. 37% of PSC now occurs in CD patients and a rising BMI in both UC and CD is contributing to new cases of NASH in both of these conditions. Liver disease in IBD is evolving, reflecting changing patterns of IBD and the obesity epidemic in the US.

2. BODY COMPOSITION IN CIRRHOTIC PATIENTS AFTER LIVER TRANSPLANTATION

Joseph T Bergerson, June-Goo Lee, Alessandro Furlan, Achuthan Sourianarayanane, Amit D. Tevar, Andrea F. DiMartini, Michael A. Dunn

Background and Aim: Sarcopenia, a strong indicator of deconditioning in cirrhosis, predicts mortality awaiting and following liver transplantation. There are no data on the impact of transplantation on progression or recovery from sarcopenia as commonly measured on abdominal CT imaging. We explored whether consistent measurable changes would occur in sarcopenia, visceral and subcutaneous adipose tissue, and bone density, all important determinants of recovery, in 63 patients (38 men, 25 women) transplanted for primary sclerosing cholangitis (PSC), nonalcoholic steatohepatitis (NASH) and alcoholic cirrhosis (AC).

Methods: We chose PSC, NASH and AC for initial study because of their low likelihood of early recurrence. We selected patients without the potentially confounding metabolic stresses of major surgery, renal failure or a critical care admission within 1 year after transplant and with archived scans available for comparison before and from 1 to 2 years after transplant. Scans were done for clinical indications including abdominal pain and biochemical abnormalities. Using transverse 5mm CT slices at L3 for segmentation analysis, we measured skeletal muscle index (SMI), visceral fat and subcutaneous fat as areas per height squared, and vertebral bone density as Hounsfield units (HU). We compared data with published standard imaging criteria for sarcopenia and osteoporosis.

Results: Sarcopenia (SMI $\leq$52.4cm^2/m^2 men, $\leq$38.5cm^2/m^2 women) was highly prevalent in 70% of patients before and 56% 1 year or more after transplant, and was markedly prominent and sustained in PSC (20 of 22 before and 21 of 22 after transplant). It showed a nonsignificant trend toward improvement in 63% of patients. Osteoporosis (<160HU) was present in 60% of patients before and 73% a year after transplant and worsened in 75%. Both visceral and subcutaneous fat was most pronounced before and continued to nonsignificantly worsen after transplant in NASH cirrhosis.

Conclusion: We found that major body composition abnormalities are common in cirrhosis and generally fail to resolve or significantly improve a year after transplantation. They appear to be important measurable therapeutic targets for improving post-transplant care. Given the limitations of our selected retrospective dataset, we suggest that prospective evaluation of serial body composition imaging as an objective indicator of treatment efficacy could help define its potential clinical value.

3. A Concept Recognition Tool to Identify the Surgical Complications of Crohn's Disease in Electronic Health Records

Visweswaran, Shyam[1]; Saul, Melissa I.[1]; Espino, Jeremy U.[1];
Levander, John[1]; Swoger, Jason M.[2]; Regueiro, Miguel[2]; Dunn, Michael A.[1, 2]

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2. Medicine, University of Pittsburgh, Pittsburgh, PA, United States.

Background and Aims: An important component of electronic health records (EHR) based clinical research involves recognizing and extracting text from clinical reports in order to identify significant findings or outcomes. For example, identifying the surgical complications of Crohn's disease (CD) in a dataset typically involves manual review of operative reports that are associated with relevant ICD9 codes to determine whether a reported event actually represented a CD surgical complication. We desired to develop a software tool to automatically extract important features from clinical text reports and apply a classification model to such features to identify if the report contained an event of interest. This study aims at identifying operative reports that describe surgical procedures related to CD. It compares the performance of a classification model that is trained using traditional ICD9 codes with that of an alternative model that is trained using Unified Medical Language System (UMLS) concepts. The UMLS is a controlled vocabulary developed by the National Library of Medicine and contains a large number of standardized medical concepts.
Methods: Operative reports of CD patients were obtained from the EHR at an academic medical center. For each report, associated ICD9 codes were obtained from discharge abstracts, and UMLS concepts were identified with a concept recognition tool called Ontology Development Enrichment (ODIE), a part of our clinical phenotyping application. The reports were manually evaluated by an expert on CD and were labeled either as CD-related surgery or non-CD-related surgery. The ICD9 codes and UMLS concepts, along with their labels, were used to train a naive Bayes classifier application. All evaluations were performed using 20-fold crossvalidation to avoid bias, and the area under the ROC curve (AUC) was used to measure performance.
Results: Of the total of 1,517 operative reports, 879 were labeled as CD-related surgery and 638 as non-CD-related surgery. The classifier trained with ICD9 codes used 42 ICD9 codes as features and had an AUC of 0.587 with a 95% confidence interval of (0.556 - 0.605). The classifier trained with UMLS concepts used 1,704 UMLS concepts as features and had an AUC of 0.891 (0.872 - 0.923). Performance was far better with UMLS concepts (Table 1).
Conclusion: A classifier tool trained with UMLS concepts achieved high efficiency and superior performance in identifying CD-related surgical events in operative reports compared with that of a classifier trained with ICD9 codes. Our finding is consistent with clinical experience that ICD9 coding for the surgical complications of CD has had limited precision and value. We suggest that wide application of automated UMLS trained free text extraction and classification has strong potential to improve the effectiveness of EHR based clinical research.

4. Electronic Health Record (EHR) Information Is Useful To Predict Clinically Relevant Outcomes in Acute Pancreatitis (AP)

Yadav, Dhiraj1; Saul, Melissa I.2; Papachristou, Georgios I.1;
Whitcomb, David C.1; Visweswaran, Shyam2; Dunn, Michael A.1, 2

1. Medicine, University of Pittsburgh, Pittsburgh, PA, United States.
2. Biomedical Informatics, University of Pittsburgh, Pittsburgh, PA, United States.

Background: Persistent organ failure (OF) has been identified as a strong predictor of clinical outcomes in AP. Presence of systemic inflammatory response syndrome (SIRS) helps in early prediction of ICU admission and OF. While administrative data are used widely to describe population distributions, the use of EHR data to predict outcomes in AP has not been well studied. We hypothesized that EHR data would be useful to predict clinically relevant outcomes in AP.
Methods: Using diagnosis codes, we identified all unique patients with a primary discharge diagnosis of AP from 2000-2009 at the University of Pittsburgh Medical Center. Patients with no available previous history, prior acute or chronic pancreatitis, organ transplant, pre-existing renal failure (serum Cr ≥ 2 or dialysis), a pancreatic cancer diagnosis [within 6 months], transfers from other institutions, and in whom SIRS data could not be retrieved by EHR were excluded. Information was retrieved using the EHR on demographic factors, etiology (using associated diagnoses codes), presence of SIRS (score of ≥2) on day 1, ICU admission, persistent OF (ICU admission ≥48 hours or serum Cr ≥2 mg/dl for ≥48 hours or dialysis), length of stay (LOS) and mortality (within 7 days, 30 days, or 90 days). The prevalence and risk of persistent OF and mortality based on SIRS and ICU admission were determined after controlling for confounding factors.
Results: The mean age of patients (n=502) was 58 ± 18 years, 56% were female, 80% were White, mean Charlson co-morbidity score was 5.2 ± 1.9 and median LOS was 6.8 days. Common etiologies were biliary (40%), idiopathic (26%) or alcohol (8%). Overall prevalence of SIRS on day 1, ICU admission ≥48 hours, and persistent OF was 38%, 11% and 13% respectively. Mortality within 7 days, 30 days and 90 days of admission was 1%, 1.2% and 2% respectively. The risk of ICU admission, persistent OF and mortality increased progressively with an increase in SIRS score from 0-4 ($p<0.05$) and when evaluated as <2 or ≥2 (Table 1). On multivariable logistic regression (Table 2), the presence of SIRS significantly increased the risk of ICU admission ≥48 hours, persistent OF and mortality after controlling for age, gender, race, comorbidity and etiology. Risk of mortality increased significantly with prolonged ICU admission (Tables 1-2). The Charlson co-morbidity score was also a significant predictor for all outcomes while increasing age predicted mortality ($p<0.05$) and had borderline association with persistent OF ($p=0.06$) and ICU admission ≥48 hours ($p=0.08$).
Conclusions: EHR data provide robust prediction of clinically relevant outcomes in AP, and present a unique opportunity to study short- and long-term outcomes and resource utilization in AP. Incorporating identification of pancreatic necrosis by natural language processing will further enhance EHR utility.

5. Inflammatory Bowel Disease and Selective Immunoglobulin A deficiency

Introduction: Selective Immunoglobulin A Deficiency (SIgAd) is one of the most common immunoglobulin deficiencies in the population. A proportion of these patients reach adulthood completely asymptomatic, while others experience recurrent sinopulmonary infections. A few case reports have been published reporting SIgAd and Inflammatory Bowel Disease (IBD). We aim to describe the prevalence of SIgAd in an IBD patient registry, as well as the rates of hospitalizations and use of biologics and immunomodulators.

Methods: Analysis of prospectively collected IBD patient registry was conducted. Patients who were tested for Immunoglobulin A (IgA) Immunoglobulin G (IgG), and Immunoglobulin M (IgM) levels comprised the study population. SIgAd was defined as serum levels <0.07g/L along with the presence of IgG and IgM in the serum. Descriptive statistics were conducted on the study population. Chi Square analysis on the number of hospitalizations was conducted. Rates of biologic and immunomodulator use were investigated as well using Fisher's exact analysis.

Results: A total of 547 patients were tested. SIgAd was found in 1% of the study population (n=6). All 6 were Crohn's Disease patients. Mean age was 36.8yrs($\pm$ 14.9yrs). These patients were 66% female (n=4). Hospitalization rates were 17%, 37%, 39%, and 58% for SIgAd, decreased IgA, normal IgA, and elevated IgA patients, respectively, over a three-year period (P=0.034). Rates for biologics were 67%, 28%, 38% and 55% respectively (P=0.037). Immunodulator rates were 50%, 50%, 57% and 62%, respectively (P=0.8).

Conclusion: The prevalence of SIgAd might be higher in the IBD population. Most cases may be present concomitantly with Crohn's Disease versus Ulcerative Colitis. Hospitalization rates were lower for IgA deficient patients, with a larger proportion of them using Biologics. These results suggest that Biologics might be protective in SIgAd patients.

6. Effect of the bile acid sequestrant Colesevelam on Health Related Quality of Life in Crohn's Disease

Chandraprakash Umapathy, Claudia Ramos Rivers, Miguel Regueiro, Leonard Baidoo, Arthur Barrie, Marc Schwartz, Jason Swoger, Michael Dunn, Katie Weyant, Andrew Watson
David G Binion

Background: Diarrhea is a common symptom in Crohn's disease (CD), often originating from ileal dysfunction/resection leading to bile malabsorption and bile salt diarrhea (BSD). Bile acid binding resins can improve symptoms in BSD. Colesevelam (COL) is the newest available bile acid sequestrant, currently FDA indicated for reduction of LDL cholesterol and improving glycemic control in type 2 diabetes mellitus. Although COL has greater affinity for bile acids, is better tolerated, has fewer GI side effects and is easily administered there are limited data regarding its use in CD treatment.

Methods: Review of observational data from consented, prospective IBD registry. CD patients treated with COL formed the study population. Demographics, Harvey-Bradshaw Index (HBI), surgical history, medications and quality of life score (SIBDQ) were extracted. COL response was determined based on HBI, diarrhea subscore and SIBDQ scores 1 year before and after starting medication.

Results: There were 91 COL treated CD patients. Mean age was 42.6 y (median 41, SD 14.2y), female 69%, 43% had smoking history. Among the COL treated CD patients 50% had ileocolonic, 41% had ileal disease, 32% had undergone cholecystectomy and 37% had used narcotics for the treatment of pain during the study period. 76% of the COL treated CD patients had undergone terminal ileal resection (TIR) prior to starting the medication. After starting COL, quality of life improved in 58% of patients; 69% showed improvement in their disease activity scores; 65% had decreased number of liquid stools (LS) per day. Only 27% of COL treated patients showed improvement in abdominal pain. Both SIBDQ and LS improved in 41.8%. Mean SIBDQ before and after starting medication was 43.5 and 45.4 respectively (SD 11.3) in the total cohort. Non-responders had a worsening in mean SIBDQ of -5.6 (47 to 41.4), whereas responders showed a 7.1 point improvement (41 to 48.1; $p = 0.024$). Females responded better to COL based on HBI scores compared to male patients (76.2% vs. 53.6%; $p = 0.031$). The majority of CD patients both with TIR and without surgery responded to COL (HBI improvement 71% vs. 63.6%, SIBDQ improved 59.4% vs. 54.5%). Following COL, SIBDQ improved in 69% of patients with CCY vs. 53.2% in those without ($p = 0.15$). COL responders (improvement in SIBDQ and/or liquid stools) had lower rates of surgery within 1 yr of starting medication compared to non-responders (8.1% vs 29.4%, $p = 0.029$). Among the TIR patients treated with COL, there were 31 with side-to-side anastomosis (STSA) and 28 with end-to-end anastomosis (ETEA). 78.6% of patients with ETEA showed improvement in HBI while taking COL compared to 54.8% for the STSA group ($p = 0.054$).

Conclusions: COL improves HRQOL and diarrheal symptoms in CD patients. Future trials of COL in treatment of CD patients with chronic diarrhea are warranted.

7. Silent Crohn's disease: Elevated C reactive protein in asymptomatic patients and risk of subsequent hospitalization.

Eric J. Vargas, Claudia M. Ramos Rivers, Miguel Reguerio, Leonard Baidoo, Arthur Barrie, Marc Schwartz, Jason M. Swoger, Matthew Coates, Michael a. Dunn, Anwar Dudekula, David G. Binion

Introduction: Crohn's disease (CD) is characterized by periods of inflammatory activity which typically corresponds with symptoms, including abdominal pain, diarrhea and fatigue and elevation of the biomarker C reactive protein (CRP). Patient-reported CD symptoms have historically guided routine care, but it is unknown whether patients feeling well with elevated CRP warrant additional diagnostic evaluation and/or escalation of treatment. We hypothesized that asymptomatic CD patients with elevated CRP ("Silent CD") are at increased risk for disease-related hospitalizations compared to individuals feeling well without objective serologic evidence of inflammation.

Methods: A prospectively collected patient registry which included demographics, short inflammatory bowel disease questionnaire (SIBDQ) scores and CRP values was analyzed. Patients with an SIBDQ score>50 (good quality of life) with a same-day CRP lab result formed the study population. Patient hospitalizations occurring up to 24 months after their initial clinic visit during the observation period were recorded. Chi-square analysis for CRP levels and hospitalizations, and univariate and multivariate logistic regression adjusting for age, gender, abdominal pain, biologic, immunomodulator and narcotic use were conducted.

Results: A total of 181 CD patients were included in the study who had a mean SIBDQ score 59$\pm$ 5.4 (SD), mean age 42 y $\pm$15y (SD) and were 54% female. CRP was elevated in 24% of these patients (n=43) who formed the Silent CD cohort. Mean SIBDQ scores were not significantly different between the CD patients who felt well/no CRP elevation and the Silent CD patients (59 vs. 58; p=0.06), but abdominal pain sub-scores were significantly different (6 vs. 5.5; p=0.01). At 24 months, 14% of the total CD patients required hospitalization (n=25). The rate of hospitalization in the Silent CD cohort was 37% (16/43) compared with 7% of the remaining patients (9/138; P<0.001). On univariate analysis, CRP elevation (OR 8.49, 95% CI 3.39-21.22 P<0.0001) was significantly associated with hospitalization. On multivariate analysis, CRP elevation (OR 6.82, 95% CI 2.50-18.58; P<0.0001) was significantly associated with hospitalizations after adjusting for covariates. Analysis remained significant when analyzing patients with SIBDQ scores greater than 55 and 60 as well.

Conclusion: CD patients who report excellent quality of life in clinic despite objective evidence of inflammation manifested by CRP elevation are at a 6-fold higher risk for hospitalization during the ensuing two years. These silent CD patients may benefit from further evaluation or closer monitoring to prevent disease related complications requiring hospitalization.

8. Sleep quality and the clinical course of Inflammatory Bowel Disease

Claudia Ramos Rivers, Eric Vargas, David G Binion, Miguel Regueiro, Leonard Baidoo, Arthur Barrie, Jason Swoger, Marc Schwartz, Michael Dunn, Eva Szigethy, David Benhayon

Background:
High quality sleep is essential for achieving optimal health, which is also true for patients suffering from inflammatory bowel disease (IBD). Sleep disturbance in IBD can be due to nocturnal bowel movements, medication side effects and disease activity, but there is limited data regarding sleep hygiene in this patient population. Data from IBD animal models suggests that disrupted sleep worsens disease activity. We sought to characterize sleep patterns in a cohort of IBD patients and correlate sleep hygiene with clinical course and disease activity.

Methods:
Patients were prospectively recruited to provide data on sleep quality using the Pittsburgh Sleep Quality Index (PSQI), a validated sleep hygiene instrument. PSQI total scores were used to categorize poor (PSQI total score >5) or good (PSQI total score ≤ 5) quality sleep. Prospectively obtained observational data was used to characterize IBD clinical status, which included quality of life assessment (short inflammatory bowel disease questionnaire (SIBDQ)), CRP levels, prescription patterns, clinic visits, patient generated telephone calls, emergency department use (ED) and hospitalizations summarized over the calendar year.

Results:
PSQI data was obtained from 444 IBD patients who formed the study population (male 45%, female 55%; Crohn's disease (CD) 62%, ulcerative colitis (UC) 38%). Poor quality sleep was identified in 53% of the IBD patients. Poor quality sleep was more common in females vs. males (60% vs. 40%; P <0.05) and more common among CD patients (68%) compared with UC (33%; P<0.005). The mean SIBDQ score of patients with poor quality sleep was 45.1± 11.2 (S.D.) compared with good quality sleep 58.0± 9.0 (S.D.) (P<0.0001). Rate of prednisone use was higher in patients with poor compared to good quality sleep (61% vs. 25%; P< 0.04). Rate of CRP elevation was higher in patients with poor compared with good quality sleep (38% vs. 25%; P<0.05). The rate of narcotic use was higher in patients with poor compared to good quality sleep (27% vs. 7%; P<0.0001). The rate of psychiatric medication use was higher in patients with poor compared with good quality sleep (50% vs. 16%; P<0.0001). There were significantly more clinic visits, hospital admissions, telephone calls (all with P<0.001) and ED visits (P<0.02) from IBD patients with poor compared with good quality sleep.

Conclusions:
Poor sleep quality is commonly found in IBD, occurring in 2/3 of CD and 1/3 of UC patients. Poor quality sleep correlates with worse IBD clinical status, as measured by biochemical inflammation, steroid use, healthcare utilization and disease related quality of life.
Improved sleep hygiene is an important goal for optimizing the quality of IBD patient care.

9. Clinical factors contributing to abdominal pain in IBD

Claudia Ramos Rivers, Eric J Vargas, Mathew Coates, Miguel Regueiro,Michael Dunn, Jason Swoger, Marc Schwartz, Arthur Barrie, Leonard Baidoo, Eva Szigethy, David G Binion.

Background: Abdominal pain is a common symptom in IBD and an important cause for clinic visits. Abdominal pain may be related to active inflammation, but the etiology can include additional factors such as surgical complications, nerve damage as well as the patients' perception of pain. At present, there is limited information regarding the clinical factors contributing to abdominal pain in patients with IBD.

Aim: Define the prevalence of abdominal pain in the IBD outpatient setting and correlating clinical factors, with a focus on patients with and without biochemical evidence of inflammation.

Methods: Observational data from a prospectively recruited IBD registry over 3 years was analyzed. The first visit encountered by each unique patient was identified. All patients provided quality of life data using the Short Inflammatory Bowel Disease Questionnaire (SIBDQ). The abdominal pain sub score was used to gauge pain (scores range from 1 "all of the time" to 7 "none of the time"). Clinic encounters with score of 4 ("some of the time") and lower were designated as "pain IBD" while encounters with scores of 5 – 7 were designated "no pain IBD." Biochemical evidence of inflammation was defined by elevated CRP drawn at the time of the clinic encounter. Information regarding demographics, treatment and co-morbidities were used in the multivariate logistic regression model.

Results: Data from 981 unique patients (52% female; mean age 42.6 years; Crohn's disease (CD) 63% ulcerative colitis (UC) 37%) was analyzed. 39% of the IBD patients (n=384) reported abdominal pain (pain IBD cohort). Biochemical inflammation was identified in 28% of the IBD patients. 38% of the pain IBD and 21% of no pain IBD had CRP elevation ($P<0.001$). Pain IBD was 71% CD while no pain IBD was 58% CD ($p<0.001$). Pain IBD was 61% female while no pain IBD was 46% female ($P<0.001$). Co-morbidity with anxiety/depression was identified in 38% of pain IBD and 20% of no pain IBD ($P<0.001$). Biologic use was present in 33% of the pain IBD group and in 26% of no pain IBD ($P<0.02$) but no difference in immunomodulator use was identified. Multivariate logistic regression identified psychiatric co-morbidity (OR 1.82), CRP elevation (OR 1.85), female gender (OR 1.53), CD diagnosis (OR 1.65), narcotic prescriptions (OR 2.05) and prednisone (OR 2.26) as clinical factors correlating with pain. When multivariate logistic regression was performed on pain IBD patients with no CRP elevation, all clinical factors remained significant.

Conclusions: Abdominal pain is encountered in one third of IBD clinic visits, and is associated with CD, active inflammation, female gender, psychiatric co-morbidity. The majority of IBD patients with pain did not demonstrate biochemical evidence of inflammation suggesting additional mechanisms underlie these symptoms.

10. Metabolic syndrome and Inflammatory Bowel Disease

Jennifer Seminerio, Claudia Ramos Rivers, Jai Behari, Annette Wilson, Katie Weyant, Miguel Regueiro, Leonard Baidoo, Arthur Barrie, Jason Swoger, Marc Schwartz, David G Binion

Introduction:
The obesity epidemic has affected patients with inflammatory bowel disease (IBD) and new data suggests that the majority of IBD patients are overweight and up to one third suffer from obesity with body mass index (BMI) > 30. Obesity is associated with systemic health problems including vascular disease (hypertension), dyslipidemia and hyperglycemia (type 2 diabetes mellitus), collectively known as metabolic syndrome. The overlap of disorders defining metabolic syndrome and IBD has not been previously characterized.

Methods:
This was an observational study from a consented, prospective IBD registry. Medical comorbidities were determined using prescription data corresponding to treatment guidelines for hypertension, diabetes and hypercholesterolemia. BMI was broken down into underweight (<18.5), normal (18.5-25), overweight (25-30), obese class I (30-35), obese class II (35-40) and obese class III (>40).

Results:
There were 1494 IBD patients analyzed (56% Crohns disease; 49% male) who had the following BMI distribution: normal (30.4%), overweight (36.4%), obese class I (18.5%), obese class II (8.6%) and obese class III (4.3%). The rates of the metabolic syndrome defining illnesses in the IBD cohort was: hypertension 23.4%; diabetes mellitus 5.8%; hypercholesterolemia 12.6%. The distribution of these disorders stratified by BM in the IBD patients:

Metabolic syndrome co-morbidities	Normal-Weight (BMI 18.5-25)	Overweight (BMI 25-30)	Obese I (BMI 30-35)	Obese II (BMI 35-40)	Obese III (BMI >40)
Hypertension (%)	15.0	20.0	32.6	36.7	44.6
Diabetes Mellitus (%)	2.6	4.0	7.6	14.1	20.0
Hypercholesterolemia (%)	6.6	12.3	15.9	21.9	27.7

	Normal-Weight (BMI 18.5-25)	Overweight (BMI 25-30)	Obese I (BMI 30-35)	Obese II (BMI 35-40)	Obese III (BMI >40)
1 comorbidities (%)	14.8	17.3	22.5	28.9	27.7
2 comorbidities (%)	3.0	7.4	12.0	12.5	13.8
3 comorbidities (%)	<1.0	1.5	3.3	6.3	12.3

Insulin resistance in metabolic syndrome is associated with decreased levels of the adipokine adiponectin, which falls with increase in BMI. We analyzed adiponectin levels in normal BMI (n=43) and obese IBD patients (n=23). There was no difference in the adiponectin levels between these two groups (nl BMI 16943.76 $\pm$ 5142 ng/ml vs obese 13771.71 $\pm$ 7891 ng/ml; p=NS), suggesting that preservation of adiponectin in obese IBD may contribute to lower levels of type 2 diabetes.

Conclusions:
Obese IBD patients are at risk for metabolic syndrome. Lower rates of diabetes mellitus in obese IBD may be related to preservation of adiponectin. Overall impact of metabolic syndrome on the clinical course of IBD has yet to be defined.

11. Clinical characteristics of inflammatory bowel disease (IBD) patients who call after hours

Claudia Ramos-Rivers; Miguel Regueiro, Michael Dunn, Eva Szigethy, Marc Schwartz, Arthur Barrie, Jana Al Hashash, Jason Swoger, Leonard Baidoo, David G Binion.

Introduction: Telephone activity logged in the electronic medical record (EMR) has recently been shown to function as an effective and easily implemented strategy to monitor clinical status in IBD patients (Clin Gastroenterol Hepatol 2014). Increased EMR telephone encounters were associated with increased inflammatory activity, abdominal pain, poor quality of life and concomitant neuropsychiatric illness and functioned as an early warning mechanism of impending emergency department (ED) use and hospitalization. This initial investigation did not characterize the time of telephone encounters, specifically after hours calls. We sought to characterize the spectrum of afterhours telephone calls and the clinical characteristics of IBD patients who call afterhours.

Methods: Prospective observational study of consented IBD patients in a natural history registry from a tertiary center for the years 2011 and 2012. The time of telephone encounters logged in the EMR was analyzed and patients calling between 5PM - 8AM were identified as after hour callers (AHC). Clinical factors associated with AHC activity were analyzed. Short inflammatory bowel disease questionnaire (SIBDQ) from each clinic visit and the pain subscore were used to assess clinical status. Demographic information, treatment, laboratories and health care utilization were analyzed on an annual basis.

Results: In 2011 there were 937 IBD patients (47% M; mean age 44.3 ±14.9y) who generated 5,500 telephone encounters, with 149 after hour calls (2.7% of phone calls). In 2012 there were 988 IBD patients (47.5% male; mean age 44.0 ±14.9y) who generated 4,691 telephone encounters, with 110 after hours calls (2.3% of phone calls). In 2011 there were 100 AHC patients (10.7% of total IBD population; 46.5% M; mean age 43.4 ± 14.4y) and in 2012 there were 90 AHC patients (9.1% of the total IBD population; 47.8% M; mean age 36.8 ± 12.2y)

Clinical factors associated with AHC activity included increased abdominal pain, poor quality of life, elevated CRP, elevated ESR and higher rates of prednisone use when compared with non-AHC IBD controls (All with $P<0.05$). Health care utilization including ER visits, hospital admissions, clinic visits and increased daytime telephone calls was higher for the AHC patients when compared with patients who did not call afterhours during 2011 and 2012. (All with a P value <0.05)

There was no difference in IBD type, gender, age, rate of psychiatric co morbidity, rate of immunomodulator and biologic use between AHC patients and IBD patients who did not call afterhours during 2011 and 2012.

Conclusions: After hour phone calls in IBD are rare, but identify approximately one tenth of patients. These AHC IBD patients are an “at-risk” subgroup with more severe disease, who are challenged with pain and difficulty coping with their illness leading to increased ED use and hospitalization.

12. ASSOCIATION OF TELEPHONE ACTIVITY WITH CLINICAL FEATURES IN INFLAMMATORY BOWEL DISEASE (IBD): A PROSPECTIVE VALIDATION STUDY

Claudia Ramos-Rivers; Miguel Regueiro, Michael Dunn, Eva Szigethy, Marc Schwartz, Arthur Barrie, Jana Al Hashash, Jason Swoger, Leonard Baidoo, David G Binion.

Introduction: Telephone activity is essential in modern society and management of complex chronic diseases, including IBD. We have previously identified that patterns of annual telephone activity are associated with active inflammation, corticosteroid use, narcotic use, poor quality of life, abdominal pain, neuropsychiatric co-morbidity ,emergency department (ED) use and hospitalization and in patients with IBD (in press, Clin Gastroenterol Hepatol 2014). Telephone activity recorded in the electronic medical record (EMR) functioned as a clinical "red flag" to identify IBD patients who are at risk of high cost ED and inpatient care. We conducted a prospective analysis of telephone activity recorded in the EMR to validate whether these initial observations held true over a distinct, multiyear time period.

Methods: Prospective observational study from a consented natural history IBD registry in a tertiary referral center. Telephone encounters logged in the EMR were analyzed during the years 2011 -2012. Patients were categorized according to the number of telephone encounters/year: 0-1 phone calls/y (low telephone encounters (LTE)), 2-5 phone calls/y, 6-10 phone calls/y and >10 phone calls/y (high telephone encounters (HTE)). Clinical characteristics, disease activity, quality of life and health care utilization were described for each category. Short inflammatory bowel disease questionnaire (SIBDQ) scores obtained at clinic visits were used to gauge health related quality of life and the pain sub-score was used to measure abdominal pain.

Results: A total of 937 IBD patients in 2011 and 988 for 2012 were included. In 2011, 47% of patients were male with a mean age of 44.4 ± 14.9y and in 2012, 47.5% were male with a mean age of 44.0 ± 14.9y. There were 5500 telephone encounters in 2011 and 4689 in 2012. Increasing annual telephone encounters in IBD were associated with female gender ($p= 0.023$), CRP elevation ($p< 0.0001$), ESR elevation ($p< 0.0001$) poor quality of life ($p<0.0001$), increased abdominal pain ($p<0.0001$), prednisone use ($p<0.0001$), psychiatric co morbidity ($p<0.0001$) and increased healthcare utilization (i.e. ED visits, hospital admissions and clinic visits) ($p<0.0001$). Similar results were found for 2012.

Conclusions: Analysis of a separate cohort of IBD patients followed over a distinct two year time period has demonstrated consistent annual patterns of telephone encounters logged in the EMR. Increasing annual telephone encounters were associated with more severe disease, chronic pain and neuropsychiatric co-morbidity contributing to poor overall clinical outcomes, particularly in the subgroup of IBD patients with HTE. This study validates the use of telephone encounters as a strategy to stratify IBD patients and identity individuals at risk for high cost health care utilization.

		0-1 phone encounter (LTE)	2-5 phone encounters	6-10 phone encounters	>10 phone encounters (HTE)
2011	% of patients	29.3	36.1	18.7	15.8
	% of telephone encounters	2.7	19.6	23.5	54.1
2012	% of patients	34.4	39.7	14.5	11.4
	% of telephone encounters	3.9	26.4	22.5	47.2

13. Characterization of autonomic dysfunction in inflammatory bowel disease (IBD): Use of a validated short self-assessment instrument for screening in a tertiary referral clinic

Claudia M. Ramos Rivers[1], Kimberly Baker[1], Jana G. Hashash[1], Miguel Regueiro[1], Eva Szigethy[2, 1], David J. Levinthal[1], Michael A. Dunn[1], David G. Binion

Introduction: Secondary autonomic nerve dysfunction is (AD) is commonly encountered in diabetes mellitus where it can contribute to gastrointestinal (GI) symptoms (i.e. gastroparesis). AD is recognized as a complication of chronic inflammatory disorders such as lupus, rheumatoid arthritis and IBD. In IBD, AD can contribute to GI functional symptoms (i.e. abdominal pain, diarrhea), fatigue, poor quality of life and increased healthcare utilization (ref J Clin Gastroenterol 2010). Characterizing the prevalence of AD in IBD has been limited by the need for specialized autonomic lab testing and/or complex screening questionnaires. An abbreviated composite autonomic symptom score, the COMPASS31, is a new short version of a validated AD self-assessment instrument which can be completed in <5 minutes. We provide preliminary data regarding the implementation of COMPASS31 to screen for AD in an IBD referral clinic. **Methods:** Prospective study of consecutive IBD patients who completed COMPASS31 in a referral clinic. COMPASS31 scores range from a lowest score of 0 to 100, with higher scores designating worsening autonomic function and includes component scores for orthostatic intolerance, vasomotor, secretomotor, gastrointestinal, bladder and pupillomotor function. A score >32.5 was used to designated AD. Linked demographic and clinical data was used for association analysis. Health related QoL was approximated using short inflammatory bowel disease questionnaire (SIBDQ) and the pain subscore which were analyzed separately. Medication use and laboratory data was obtained on all patients. **Results:** 124 IBD patients completed the COMPASS31 (41.1% males with mean age 41.2 ±13y; 58.9% females with mean age 42.31±13.6y). The majority of patients had Crohn's disease (61.3%), 19.4% had ulcerative colitis and 2.4% other. COMPASS31 scores ranged from 1.3 to 67.1; mean 27.1 ±16 SD. Forty two IBD patients (34%) had AD. Higher ESR was more common in AD IBD pts vs no AD (88% vs. 63%; $p<0.001$). Narcotics use was higher in AD IBD patients (69.6% vs. 34%; $p<0.01$). Prednisone prescription was higher in AD IBD vs no AD (71% vs 55%; $p<0.05$). Antidepressant use was higher in AD IBD vs no AD (52% vs28%; $p<0.001$). Psychiatric co-morbidity was more common in AD IBD vs no AD (56% vs. 22%; $p<0.01$). Patients with AD had a lower QoL (mean SIBDQ 39.01 ±10.1 vs. 51.18 ±10.9; $p<0.0001$) and had increased abdominal pain (3.76±1.2 vs.5.2 ±1.3; $p<0.0001$). AD had worse QoL with or without concurrent inflammation compared to no AD (with CRP elevation 34.7 ±9.4 vs. 48.5 ±12.3; $p<0.001$; without CRP elevation 47.2 ±9.3 vs. 54.8 ±8; $p<0.01$). There was no difference in age, gender, IBD type, disease duration, biologic and immunomodulator use in patients with and without AD. Patients with AD IBD and history of bowel resection had a lower SIBDQ score vs no AD and history of bowel resection (40.21 ±11.9 vs 49.07 ±11.6; $p<0.005$) **Conclusions:** COMPASS31 was readily implemented in the workflow of the IBD referral clinic. COMPASS31 scores identified 1/3 of referral IBD patients at risk for AD. AD IBD is associated with poor QoL regardless of the presence of serological inflammation. AD IBD patients also had increased abdominal pain and increased use of narcotics. Screening for AD in IBD is warranted as this may contribute to refractory symptoms and poor QoL.

14. Impact of benign joint hypermobility syndrome on inflammatory bowel disease

Nitin Aggarwal, Kim Baker, Claudia Ramos Rivers, Jana Al Hashash, Miguel Regueiro, Michael Dunn, David G Binion

INTRODUCTION:

Benign Joint Hypermobility Syndrome (BJHS) is a common, heritable, multisystem disorder that can cause dysfunction and/or pain in the musculoskeletal, autonomic nervous, and gastrointestinal (GI) systems. BJHS is characterized by hypermobile joints (i.e. patients are double jointed) and this may correlate with tissue laxity/increased compliance in internal visceral organs including the luminal GI tract. Recent data show an increased incidence of BJHS in patients suffering from functional GI disorders as well as Inflammatory Bowel Diseases (IBD) (Zerate and Vounotrypidis). We sought to characterize the differences in clinical presentation of IBD between patients who have BJHS and those who do not.

METHODS:

Prospective evaluation of IBD patients in a tertiary referral clinic. BJHS was diagnosed using the previously validated Brighton Criteria and Beighton Score. IBD clinical data were abstracted from a prospective patient registry, including healthcare utilization (i.e. Emergency Room (ER) visits, telephone calls, hospitalizations, and clinic visits), health related quality of life (short inflammatory bowel disease questionnaire (SIBDQ)) scores obtained at clinic visits, and abdominal pain scores (subscore from the SIBDQ) from 2009-2012. We also evaluated their psychiatric comorbidities, medications and laboratory data including rates of elevation in biochemical markers of inflammation (ESR and C-Reactive Protein (CRP)).

RESULTS:

99 IBD patients (52 female (53%), 47 male (47%)) were screened, and 30 (30%) met criteria for BJHS. IBD patients with BJHS were significantly more likely to be female. 73% of our sample had Crohn's disease and 24% had ulcerative colitis (UC), but patients who were BJHS positive, were more likely to have UC compared to Crohn's disease. BJHS patients were also more likely to be younger by a mean difference of 8 years (95% CI 1.98,13.89).

IBD patients with BJHS had significantly ($P<0.05$) better SIBDQ scores (with a mean increase in 4.15 points [95% CI 2.65, 5.65]). In addition, they tended to have decreased ER visits, hospitalizations, and clinic visits. However, the BJHS IBD patients were significantly ($P<0.05$) more likely to be on biologics, immunomodulators, prednisone, and narcotics as well as having an elevated ESR.

Our patients with BJHS also were significantly ($P<0.05$) more likely to be diagnosed with a psychiatric disorder or be prescribed psychiatric medications.

CONCLUSION:

BJHS IBD patients may have more severe disease as approximated by their need for immunomodulators, biologic agents and prednisone, but also had a robust response to therapy with better QoL and decreased healthcare utilization compared with IBD controls. The relationship between musculoskeletal

15. Patterns of Antibiotic Exposure and Clinical Disease Activity in Inflammatory Bowel Disease: A 4 Year Prospective Study

Jana Al Hashash, Claudia Ramos Rivers, Miguel Regueiro, Arthur Barrie, Marc Schwartz, Leonard Baidoo, Jason Swoger, Michael Dunn, David G Binion.

Background and Aim: The normal intestinal microbiota plays beneficial roles in protection against pathogen invasion, development of the immune system and in nutrition but is also felt to play a central role in the pathogenesis of inflammatory bowel disease (IBD). Antimicrobial treatment is known to cause both short- and long-term changes in the composition of the normal human microbiota. The relationship between patterns of antibiotic use and overall clinical behavior in IBD has not been explored. We sought to prospectively characterize patterns of antibiotic use (for IBD and non-IBD issues) and clinical IBD activity in a cohort of pts followed over 4 years.

Methods: Prospective observational study from a longitudinal IBD natural history registry between 2009 and 2012. Demographic information, disease type, quality of life (QOL) as measured by SIBDQ, and healthcare utilization data was collected. Patterns of IBD related hospitalizations, clinic visits, telephone calls, and emergency department (ED) visits were analyzed. Antibiotic prescriptions were identified using electronic medical record data and were categorized by drug class (antihelminths, macrolides, quinolones, penicillin, cephalosporin, etc). Laboratory data was analyzed. Cumulative rates over the 4 year study period were compared.

Results: A total of 718 pts followed over 4 years were included (47.6% male, mean age 46.7±15.2y SD). Most pts (59.9%) had CD while 38.6% had UC, and 1.5% were indeterminate. Four-hundred seventy-six (66.3%) pts were exposed to antibiotics during the 4-year study period while 33.7% did not receive antibiotics. There was no difference in the gender or age of pts who received antibiotics compared to those who did not. The antibiotic exposed group was more likely to include CD pts (63% vs. 53.7%; p 0.05), require narcotics (43.7% vs. 14.9%; p<0.0001), receive anti-depressant therapy (43.1% vs. 18.6%; p<0.001) and require prednisone (52.7% vs. 31%; p<0.0001). There was no difference in the rates of immunomodulator use between groups, but antibiotic exposed pts were more likely to be on biologic therapy (52% vs. 36.5%; p<0.0001). Antibiotic exposed IBD pts had higher healthcare utilization as shown in Table 1. Antibiotic exposed IBD pts compared with non-antibiotic exposed IBD had a lower QOL (mean SIBDQ 50.2±11.5 vs 56.4±9.5; p<0.0001) and higher rates of CRP elevation (49.2% vs 31.8%; p<0.0001). There were 3,559 total antibiotic prescriptions; most common were metronidazole (23.7%), quinolones (22.9%), macrolides (10.4%), penicillins (9.8%) and cephalosporins (8.4%).

Conclusion:
A majority of IBD pts receive antibiotic treatment and these exposed individuals demonstrate a more severe clinical course, but the causative nature of this association is unclear. Further examination of antibiotic treatment on gut microbiome and IBD natural history is warranted.

Table 1.

	Antibiotic Exposed (n=476)	No Antibiotics (n=242)	p-value
Clinic Visits	10.9±8.9	6.5±4.2	0.0001
Telephone Encounters	27.0±25.7	14.8±11.4	0.0001
ED Visits	2.7±7.2	0.7±3.7	0.0001
Hospitalizations	1.6±3.1	0.4±1.2	0.0001

16. The longitudinal impact of serotonin reuptake inhibitors on quality of life and disease activity in adults with inflammatory bowel disease (IBD)

Claudia M. Ramos Rivers[1], David G. Binion[1], Ada Youk[3], Miguel Regueiro[1], Michael A. Dunn[1], Jana G. Hashash[1], Marc Schwartz[1], Leonard Baidoo[1], Arthur Barrie[1], Jason M. Swoger[1], Eva Szigethy[2,]

Background: Pts with IBD have high rates of anxiety and depression often treated by medical providers with antidepressants. While antidepressants have been shown to be well-tolerated and to be associated with improved IBD course in small cohorts, the longitudinal impact of specific antidepressants on health-related factors (quality of life (QOL) and IBD activity) has not been assessed in a large clinical cohort.

Methods: Prospective observational study of consented IBD pts using a longitudinal natural history registry over 4 years. Electronic medical records (EMR) were used to identify frequency and classes of antidepressant use (i.e. serotonin reuptake inhibitors (SSRI), serotonin noradrenergic reuptake inhibitors (SNRI), and bupropion). For the most frequently used antidepressants, we evaluated differences in QOL (SIBDQ) and IBD activity (HBI/UCDAI) between pts taking antidepressants and those who did not during that same 4 year period. Mixed effects logistic regression models were used to test whether there was a difference in the proportions of poor QOL and active IBD by SSRI use, time, and their interaction. Models were also fit controlling for age, sex, bowel resection, narcotics, prednisone, and biologics to assess whether the effect of SSRI changed.

Results: A total of 855 IBD pts were included. 48.3% were male (mean age 47 ± 15), 58.8% had Crohn's disease, 41.2% had ulcerative colitis and 46.7% had history of GI surgery. During the 4 year period, 31.2% of pts had taking narcotics, 43.5% had been on biologic agents and 44.3% on systemic steroids.

SSRI was most common class used across all 4 years. The majority of antidepressants were prescribed by gastroenterologists or primary care physicians. Few pts were receiving psychotherapy/behavioral interventions.

There was a difference in proportion of poorer SIBDQ (OR=22.88, 95% CI=8.89-58.89, p<0.0001) and higher IBD activity (OR=6.34, 95% CI=2.91-13.80, p<0.0001) in those taking SSRIs vs. those who did not but not in proportion with higher inflammation (CRP) in those taking SSRIs(OR=1. 78, 95% CI= 0.92-3.42, p=0.09). Narcotics use, steroid use and surgery reduced the ORs for SSRI, suggesting that the increased risk of poorer outcomes may also be due to confounding and not SSRI use alone. SIBDQ improved and IBD activity decreased over time in both groups.

Conclusions:

1) SSRI is the most commonly prescribed antidepressant class in IBD, most often for anxiety, depression and functional pain and was not associated with a protective effect on IBD activity or QOL.
2) Mean IBD activity decreases and QOL improves over time, independent of SSRI use.

17. Prospective Analysis of Bile Acid Sequestrant Therapy in Inflammatory Bowel Disease

Chandra Umapathy, Claudia Ramos Rivers, Miguel Regueiro, Arthur Barrie, Jana Al Hashash, Marc Schwartz, Jason Swoger, Leonard Baidoo, Michael Dunn, David G Binion.

Background: Bile acid malabsorption resulting in bile salt diarrhea (BSD) is a common cause of morbidity in pts with inflammatory bowel disease (IBD). Bile acid sequestrants including cholestyramine, colestipol, and colesevelam help control symptoms by binding bile salts intraluminally in the intestine. They are often prescribed in clinical practice but there is limited data on their patterns of use, efficacy, and impact on quality of life.

Methods: Prospective observational study of consented IBD pts in a natural history registry from a tertiary clinic. Pts with bile acid sequestrant exposure (BASE) during 2009 – 2012 formed the study population. Demographics, medication history, patterns of health care utilization and quality of life (SIBDQ) scores were analyzed.

Results: Out of 718 IBD pts, 225 had BASE over the 4 year study period (exposure rate 31.3%). Mean age was 46.6 yrs. There was no difference in exposure between genders (p 0.2). 74% of BASE patients had Crohn's disease (CD) ($p < 0.001$). BASE pts had more CRP elevation (51.6% vs 39.6%, p 0.003), biologic exposure (56.2% vs 42.5%, $p < 0.001$), immunomodulator exposure (64.9% vs 52.3%, $p < 0.001$), prednisone exposure (55.6% vs 40.8%, $p < 0.001$), narcotics exposure (45.5% vs 27%, $p < 0.001$), clinic visits (13 vs 7.7, $p < 0.001$), telephone encounters (33.2 vs 17.8, $p < 0.001$), ED visits (3.8 vs 1.3, $p < 0.001$), and hospitalizations (2.3 vs 0.7, $p < 0.001$) over 4 years compared with . Their mean SIBDQ score was lower (46.9 vs 54.7, $p < 0.001$). Evaluating CD pts only, there was no difference in biologic exposure between the groups (p 0.27) but the other trends were maintained. Interestingly, post-operative CD pts with BASE had lower narcotics exposure (35% vs 52%, p 0.006) whereas there was no difference between groups in non-operative patients (p 0.67). BASE was higher among CD pts when compared to non-CD pts (63% vs 20.5%, $p < 0.01$). Non-CD pts with BASE had more CRP elevation and prednisone exposure (p 0.03), while there was no difference in biologics and immunomodulators exposure (p NS). They had higher health care utilization in terms of clinic visits, telephone calls, ED visits, and hospitalizations ($p < 0.01$). Their mean SIBDQ score was lower as well (48.5 vs 55.5, $p < 0.001$).

Conclusions: Bile acid sequestrants are an important class of medications which help manage symptoms in IBD. Pts with BASE in general had more advanced disease as evidenced by higher rates of CRP elevation, biologics, immunomodulator, and prednisone exposure, along with lower mean SIBDQ scores. Post-operative CD pts with BASE had lower narcotics exposure, suggesting bile acid sequestrants should be considered before narcotics in managing pain symptoms in this group of patients. Further studies are needed to determine the optimal use of bile acid sequestrants and their impact on quality of life in IBD.

18. Unconjugated Hyperbilirubinemia Is Inversely Associated With Modified Hepatitis Activity Index in Chronic Hepatitis C

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Background and Aim: Two recent studies reported an inverse association of elevated unconjugated bilirubin (UCB) with the severity of nonalcoholic fatty liver disease (NAFLD). Antioxidant cytoprotection by UCB was suggested as a mechanism. There are no reported data concerning UCB and liver injury in other necroinflammatory diseases. We evaluated UCB in 698 patients having a liver biopsy for chronic hepatitis C (CHC) with the aim of assessing a potential association of UCB with CHC inflammation. Methods: We studied 698 patients with a liver biopsy from 2005 to 2012 for CHC who also had total and UCB recorded. We assessed the association of UCB with the modified hepatitis activity index (MHAI), fibrosis score, aspartate aminotransferase (AST), and alkaline phosphatase (ALP) as continuous variables, and with the presence of cirrhosis. We determined the occurrence of UCB >1mg/dL in 1270 CHC patients without a biopsy. Results: UCB was >1mg/dL in 112 (16.0%) of the 698 CHC patients who had undergone a liver biopsy. Their mean MHAI, 3.5 +2.7, was lower than that of the 586 patients with UCB <1mg/dL, 4.6 +1.9 ($p = 0.0001$). UCB was negatively correlated with MHAI (rho = -0.177, $p < 0.001$). As expected for a laboratory parameter associated with advanced liver disease, UCB >1mg/dL was positively associated with AST, ALP, fibrosis score, and cirrhosis. In a multivariate analysis, UCB >1mg/dL trended towards significance with MHAI (OR 0.85; 95% CI 0.73, 1.00; $p = 0.0547$). There was no association with age, AST and ALP, and a positive association with fibrosis score (OR 1.45; 95% CI 1.23,1.7; $p < 0.0001$). We could not determine presence or absence of Gilbert's syndrome because of the coexistence of liver injury and absence of uniform data to exclude hemolysis. Genetic testing was not performed. Occurrence of UCB >1 mg/dL was present in 188 (14.6%) of the 1270 unbiopsied CHC patients. Conclusion: The inverse association of UCB with inflammation in CHC adds to and strengthens the same association reported earlier for NAFLD. Further prospective research is needed to confirm these observations and may suggest an exploitable therapeutic potential.

Appendix 7 – Full Papers Published and in Review (in Addition to Appendix 5)

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Geriatric Inflammatory Bowel Disease: Phenotypic Presentation, Treatment Patterns, Nutritional Status, Outcomes, and Comorbidity

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Abstract

Background and Aims The U.S. population is aging and the burden of geriatric inflammatory bowel disease (IBD) patients has increased. Systematic data describing pheno- typic presentation, treatment regimens, outcomes and comorbidities in elderly IBD patients is limited. We per-

formed a retrospective observational study of IBD patients age C65 followed in a 20-hospital system to determine patterns of phenotypic presentation, treatment, polyphar-

macy, nutritional status and comorbidity.

Methods Data were extracted from electronic medical record based on ICD-9 coding/indexed terms on Crohn's disease (CD) and ulcerative colitis (UC) patients.

Results A total of 393 geriatric IBD patients were iden- tified (49.1% males; 50.9% females; 61.8% UC; 38.2% CD;

73.4 ± 6.6 years old). Younger age at diagnosis of CD

(B64) was associated with greater prevalence of small bowel surgeries (63.6%) compared with those diagnosed after age C65 (20.9%) (p \ 0.005). Fistulizing/penetrating disease was frequent in patients diagnosed with CD at a younger age (43.6% compared to 7%) (p \ 0.005). IBD maintenance treatment included: 44% 5-ASA agents;

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31.6% maintenance prednisone (defined as C6 months treatment duration); 4.8% steroid suppositories; 5.6% 6MP/ azathioprine; 1.3% methotrexate; 1.3% adalimumab; 1.3%

infliximab; 9.4% loperamide/diphenoxylate/atropine; 0.5% had no IBD medications. Longer duration of CD disease correlated with vitamin B12, vitamin D and iron deficiency. Conclusion Geriatric patients diagnosed with CD earlier in life had greater small bowel involvement compared with new onset geriatric CD. There is low utilization of immu- nomodulator and biologic agents in geriatric IBD patients. Duration of CD correlates with nutrient deficiency. Pro- spective studies are warranted in this respect.

Keywords Inflammatory bowel disease • Geriatric • Elderly • Aging • Nutrition • Immune modulators • Polypharmacy • Malnutrition • Vitamin B12 • Vitamin D

Introduction

The U.S. population is aging, with 13% of Americans currently over age 65, and the geriatric population is pro- jected to rise to 20% by 2030 [1]. The effect of aging on chronic illness, including IBD, is not defined. The impact of aging on IBD may be significant, as a recent survey of U.S. hospital discharges suggested that geriatric IBD patients accounted for a disproportionate number of admissions, with 25% of all IBD-related hospitalizations in 2004 [2].

Previous studies have suggested that IBD in elderly patients is different from the disease seen in younger indi- viduals, arguing for two variant disease phenotypes. Some studies have identified lower requirements for immuno- suppression in elderly IBD patients, suggesting a more mild disease course [3]. Conversely, elderly IBD patients have an increased rate of postoperative complications along with an increased length of hospital stay and increased operating room time. This negative effect of age persists when adjusted for comorbidity and immunosuppressive therapy [4]. A recent study examining the effect of age on hospital outcomes using the Nationwide Inpatient Sample by Ananthakrishnan et al. [2] revealed elderly patients were less likely to be hospitalized with fistulizing or structuring disease. Even after adjusting for comorbidity, they had higher in-hospital mortality, and older patients with fistu- lizing CD were more likely to undergo surgery [2]. This study also showed that geriatric IBD patients who under- went surgery had a longer postoperative stay, higher hos- pital charges and increased operating room time compared with younger patients [2].

We sought to better define the clinical spectrum of geriatric IBD at the present time. To achieve this goal, we evaluated a comprehensive electronic medical record (EMR) employed by a 20-hospital health care system to identify geriatric IBD patients and determine patterns of phenotypic presentation, surgical and medical treatments, polypharmacy, nutritional deficiencies and comorbidity.

Methods

EMR Dataset

Our research strategy for characterizing geriatric IBD used EMR data from a large healthcare system which incorporated clinical information from a 20-hospital setting (both aca- demic and community hospitals) of University of Pittsburgh Medical Center (UPMC), including urban, suburban and rural health care facilities, located in Allegheny County, Pennsylvania, USA. Patient data were collected from January 1, 1991 through December 31, 2010 from IBD patients who

were C65 years of age. UC and CD were identified using

ICD-9 coding for clinical encounters (556, 556.5, 556.6,

556.9, 555, 555.0, 555.1, 555.9). Patients who were labeled to have other forms of colitis (i.e. infectious colitis, micro- scopic colitis, diverticulitis, etc.) in addition to IBD were not included in the sample study. The decision to exclude patients was based on de-identified EMR chart review. The diagnosis was confirmed by chart review after data were extracted from ICD-9 codes.

Geriatric IBD patients were identified through the institution's medical record data repository, the Medical Archival Retrieval System (MARS). This repository con- tains whole-text medical records and integrates information from central transcription, laboratory, pharmacy, finance, administrative, and other departmental databases through- out the UPMC hospitals and clinics [1]. To meet HIPAA guidelines and insure patient confidentiality, all data were

de-identified using a program which specifically removes protected health information DE-IDTM (University of Pittsburgh, Pittsburgh, PA) and an honest broker system. This study met the criteria for exemption of informed consent by the University of Pittsburgh Institutional Review Board. For the purpose of this study, data were limited to outpatient clinics, procedures, surgical treat- ments and hospitalizations in the 20-hospital setting including patients seen by a wide spectrum of providers including gastroenterologists and Internal Medicine/Family Practice physicians.

The variables which were collected included: date of birth, gender, race, family history of IBD, disease location, surgery data, duration of hospital stay, medications, nutri- tional deficiencies, comorbid conditions, outcomes and mortality. Comorbid illnesses were identified using a modification of the Charlson comorbidity index by Romano et al. [5, 6]. All data abstraction was performed by chart review in addition to the ICD-9 designation by medical coders. Clinical notes included emergency department records, history and physicals, inpatient docu- mentation, details of surgeries, discharge summaries and/or outpatient clinic notes. The individual patient diagnoses were categorized as comorbidities as described in the Charlson comorbidity index, and comorbidity scores were calculated [5, 6]. Patients on chronic maintenance medi- cations were determined by pharmacy refills over a 6-month period. Medications included current and prior chronic exposure.

Nutritional deficiencies were identified by whole text evaluation of documentation in progress notes and review of clinical laboratory values. Nutritional deficiencies were calculated from patients who had complete data sets.

Patients with iron deficiency were defined as having low serum iron level (B28 lg/dl) with concomitant low ferritin level (B60 ng/ml). We used a higher reference level for ferritin, as it may be high in inflammatory states [7]. Overt vitamin D deficiency was defined as a 25-OH vitamin D levels below the clinical range (B9 ng/dl), while vitamin B12 deficiency was defined as serum level B211 pg/ml.

Statistical analysis was performed using SPSS software (SPSS Statistics 17.0, Inc., Chicago, IL, USA). The chi- square test for independence was used to determine the relationship and frequencies between two categorical variables. Differences between the mean scores on con- tinuous variables for two different groups of subjects were assessed using independent samples t test. Analysis with Pearson correlation with a two tailed test for significance was used to describe the strength and direction of the linear relationship between two variables. Values of p \ 0.05 were regarded as significant. Analysis was performed on the population where complete data were available.

Results

Geriatric IBD Patient Demographics

We identified a total of 7,011 unique IBD patients who had been followed in our health care system at the time of the data search. Among these individuals, there were a total of 452 patients identified who were born prior to 1944 using the ICD-9 coding for IBD. Among these patients, there were a total of 59 individuals who were identified as having other forms of colitis (i.e. diverticulitis, etc.) and these were not included in this analysis. Thus only 393 (5.6%) of the IBD patients followed in our health care system met criteria for geriatric IBD. The ethno-demographic back- ground of these geriatric IBD patients has been included in

Table 1. Mean age of the patients was 73.4 ± 6.6 years

(mean ± SD) and duration of IBD was 11.7 ± 13.7 years (mean ± SD; range 0–50 years). Of the geriatric IBD patients, 193 (49.1%) were males and 200 (50.9%) were

Table 1 Demographic characteristics of geriatric patients with inflammatory bowel disease (IBD) from a 20-hospital health care system

Characteristics Percent

of patients

females. Two hundred forty-three (61.8%) elderly patients had diagnosis of UC and 150 (38.2%) had CD; 259 (65.9%) were diagnosed to have IBD before age 64 and 134

(34.1%) had diagnosis C65. One hundred fifty-six (64.2%)

were diagnosed to have UC B64, while 87 (35.8%) were diagnosed after age 65. One hundred three (68.7%) had pre-existing diagnosis of CD at age B64 years and 47 (31.3%) were diagnosed with CD after age C65 years.

Family history of IBD was identified in 5.2% of the male geriatric IBD patients and 4.5% of the females (p = NS). There was no difference in the duration of IBD

(years) in males (11.8 ± 14.1 years [mean ± SD]) and females (11.5 ± 13.4 years; p = 0.91).

Phenotypic Presentation and Bowel Surgeries in Geriatric IBD

Phenotypic presentation in geriatric UC was as follows: ulcerative proctitis (28.4%), ulcerative proctosigmoiditis (11.4%), left-sided/distal ulcerative colitis (14.3%), panco-

litis (45.9%).

Patterns of bowel surgeries in the geriatric UC cohort included proctocolectomy with ileostomy (60.6%), hemi-colectomy (14%), and ileocolectomy/partial colectomy (12.7%). Colectomy with ileal pouch-anal anastomosis was found in 6.6% and Hartmann closure with colostomy in 6.1%.

Anatomic segments involved with CD in our geriatric cohort included: esophagus/stomach/duodenum (2%), small bowel (52.1%), colon/recto-sigmoid/anal (25.7%), and internal and perirectal fistulas (20.2%). Patterns of opera- tions in geriatric CD were small bowel surgery/resection (38%), ileostomy (26.6%), large bowel surgery/reanasto- mosis (24.1%), colostomy (3.1%) and lysis of adhesions (8.2%). Phenotypic presentation has been described in Table 2 and surgeries are mentioned in Table 3.

IBD type Age at diagnosis

Table 2 Phenotypic presentation of the geriatric inflammatory bowel

disease (IBD)

B64 years C65 years

Characteristics Percent

UC (N = 243) 64.2% (N = 156) 35.8% (N = 87)

CD (N = 150) 68.7% (N = 103) 31.3% (N = 47)

Ulcerative colitis (N = 243)

of patients

Family history of IBD

Males 5.2%

Females 4.5%

Charlson comorbidity index

Ulcerative proctitis 28.4

Ulcerative proctosigmoiditis 11.4

Left sided/distal Ulcerative colitis 14.3

Pancolitis 45.9

Crohn's disease (N = 150)

Esophagus/stomach/duodenum 2

Small bowel 52.1

Colon/recto-sigmoid/anal 25.7

Internal and perirectal fistulas 20.2

Table 3 Patterns of bowel surgeries in the geriatric inflammatory bowel disease (IBD) cohort

Characteristics Percent

of patients

Ulcerative colitis Proctocolectomy with ileostomy

60.6

Hemicolectomy 14

Ileocolectomy/partial colectomy 12.7

Colectomy with Ileal pouch-anal anastomosis 6.6

Hartmann closure with colostomy 6.1

Crohn's disease

Small bowel surgery/resection 38

Ileostomy 26.6

Large bowel surgery/reanastomosis 24.1

Colostomy 3.1

Lysis of adhesions 8.2

Younger age at diagnosis of CD (B64) was associated with greater prevalence of small bowel surgeries (63.6%) compared with small bowel surgery in those diagnosed after age C65 years (20.9%) (p \ 0.005). Age at diagnosis did not influence the prevalence of large bowel involve- ment with UC (32.7% compared to 32.6%, p = NS) or the frequency of large bowel surgery (50.9% compared to 39.5%, p = NS). Fistulizing and penetrating disease was much more frequent in patients who were diagnosed at a younger age (43.6% compared to 7%; p \ 0.005).

Operative mortality was noted in 12 (5%) geriatric UC patients during the surgical admission. Peri-operative mortality occurred among 10 (6.6%) geriatric CD surgical admissions. The most common cause of IBD related death

in both the cohorts was perforation and sepsis. Length of stay for the UC surgery admissions was 10.9 ± 11.4 days (SD) and CD was 8.7 ± 8.5 days.

Patterns of Geriatric IBD Medication Use

Medication usage in the geriatric IBD patient population was analyzed. We initially determined patterns of IBD medications, specifically focusing on maintenance therapy

defined as use of a drug for C6 continuous months. Patterns

of medication usage at the most recent encounter available were reported. Five aminosalicylic acid (5ASA) agents

reasons other than IBD (chronic obstructive pulmonary disease) and were not included in the findings. We also found only one geriatric patient on budesonide, but this individual was not included in the 393 patient IBD cohort due to exclusion criteria.

Chronic use of steroid suppositories was identified in 19 (4.8%) geriatric IBD patients. Dose of maintenance pred- nisone and the percentage of patients receiving this regi- men have been described in Table 4.

Thirty (24.2%) geriatric IBD patients on chronic steroid maintenance therapy were on concomitant calcium/vitamin D supplementation and 12 (9.7%) were on bispho- sphonates/Raloxifene. Forty-one (33.3%) patients on pred- nisone had diagnosis of coronary artery disease while 31 (25.2%) had congestive heart failure.

Immunomodulator use was significantly low in the geriatric IBD patient population. Purine analog mainte- nance therapy with either 6 mercaptopurine or azathioprine was used in 22 (5.6%) patients and 5 (1.3%) were on methotrexate. Two patients on Azathioprine developed liver abscess and were discontinued. Biologic therapy in the geriatric IBD patient population was also low, with 5 (1.3%) patients receiving anti-TNF therapy with the sub- cutaneous agent adalimumab and 5 (1.3%) were receiving infliximab. The use of ant-TNF therapy was seen after the year 2000, which goes along with the FDA approval dates. Thirty-seven (9.4%) patients were on loperamide/diphe- noxylate/atropine. Two (0.5%) geriatric IBD patients identified in our center were on no IBD maintenance medications.

Older age at diagnosis of IBD (C65 years) was associ-

ated with higher use of steroids compared with those who were diagnosed at age B64 years; similarly, 65 (52.4%) IBD patients were on prednisone compared with 59 patients (47.6%); p \ 0.005. Elderly diagnosed with IBD

at age C65 years were also on higher average dose of

prednisone 8.2 ± 10.5 compared with those diagnosed at age B64 years (2.2 ± 3.4), p \ 0.005. A total of 36.3% of the patients treated with prednisone were seen during the period 1991–2000, while 63.7% were treated during 2001–2010.

Table 4 Steroid use in geriatric inflammatory bowel disease (IBD)

were most commonly used for maintenance therapy in the geriatric IBD cohort, with 173 (44%) patients taking

IBD age group (years) Average dose of

prednisone (mg/day)

Percent steroid use

medications from this class. Sulfasalazine was the most commonly prescribed aminosalicylate accounting for over half of the 5ASA usage. Chronic corticosteroid treatment was identified in 124 (31.6%) patients. Again, all of these patients had received prednisone for over a 6-month time

65–70 17.2 43.1

71–75 17.6 23.9

76–80 21.7 19.3

81–85 17.0 12.5

86 and above 10.0 1.1

period. Two patients were on maintenance prednisone for

5-ASA, biological therapy, purine analog maintenance and anti-motility agents use were not significantly different in geriatric patients with younger age at diagnosis of IBD

(B64 years) when compared to those having diagnosis

when they were older: 66 (38.2%) patients diagnosed to have IBD C65 were on 5ASA compared with 107 (61.8%) who had IBD at B64 years (p = 0.16). No patients with IBD diagnosis at C65 years of age were on adalimumab compared to 5 (3%) with diagnosis B64 years (p = 0.10). Similarly, no patients with IBD diagnosis at C65 years were on infliximab compared with diagnosis B64 (5 [3%], p = 0.10). Purine analog maintenance use consisted of 9 (40.9%) patients with diagnosis of IBD C65 and 13 (59.1%) for diagnosis B64 (p = 0.50). Use of loperamide

and diphenoxylate/atropine was found, respectively, in 12 (34.2%) C 65 and 25 (67.6%) B 64 (p = NS).

Polypharmacy has been recognized as a major compli- cating factor in geriatric medicine, as iatrogenic complica- tions associated with drug adverse reactions and drug–drug interactions will occur more often in elderly individuals [8]. We defined polypharmacy as mild (regular use of 3–4

medications) and major (regular use of C5 medications) [8].

Polypharmacy included a list of all medications docu- mented in the EMR (both prescription and over the counter

medications). The mean number of drugs in the geriatric IBD population was 7.0 ± 3.5 agents taken on a regular basis. There was a weak negative correlation between the number of medications and duration of CD (r = -0.093, p \ 0.005). Similar findings were not appreciated in the UC

cohort (r = -0.06, p = 0.54). The percentage of geriatric

IBD patients with major polypharmacy (C5 medications) was 21.7% while those on C3 medications were 94.3%.

Nutritional Deficiencies in Geriatric IBD

Specific nutritional deficiencies associated with the geri- atric population include vitamin B12 (cyanocobalamin) and vitamin D deficiencies [9, 10]. Nutritional deficiencies in vitamin B12, iron and vitamin D are commonly encountered in patients with IBD [11–15]. The impact of advanced age on these nutritional parameters in the geri- atric IBD patient population has not been defined. Sixty- five patients did not have complete nutritional lab results and were excluded from the study. Nutritional deficiencies were calculated from patients who had complete data sets (203 with UC, 125 with CD).

A total of 17.6% of geriatric IBD patients (18% CD; 17.3% UC) were found to have vitamin B12 deficiency, which was similar to published rates of vitamin B12 defi- ciency identified in a tertiary referral adult IBD population [12]. In addition, 17.6% of our cohort (13.3% CD; 20.2%

UC) had iron deficiency, while 15.3% (11.3% CD; 17.7% UC) had vitamin D deficiency. We identified the

prevalence of iron and vitamin D deficiencies in the IBD cohort to be less than published studies [15, 16].

We also compared nutritional deficiencies in elderly IBD patients with the duration of disease. There was a significant

difference in disease duration comparing geriatric CD patients with vitamin B12 deficiency (22.6 ± 14.1 years) and those without deficiency (12.5 ± 14.4 years; p = 0.02). Likewise,

duration of CD was significantly longer in geriatric CD patients with iron deficiency (21.9 ± 16.9 years) compared with patients without iron deficiency (12.8 ± 13.9 years; p = 0.03). The same pattern held regarding duration of dis-

ease in geriatric CD patients with vitamin D deficiency (28.9 ± 14.0 years) and those without deficiency (12.8 ±

14.1 years; p = 0.003). Similar correlation was not observed

in patients with geriatric UC (p [0.05). Comorbidity in the Geriatric IBD Population

Comorbid illness is frequently encountered in geriatric medicine which poses a major challenge for management. In our geriatric IBD cohort, the majority of patients suffered from multiple comorbid illnesses (Table 1). The most common comorbidities included cardiovascular illness, pulmonary disease and diabetes mellitus. Among the geri- atric IBD patients, there were 33.8% who had coronary artery disease (CAD), 22.6% with chronic lung disease (chronic lung disease was defined as patients having one of the following diagnoses: obstructive lung disease, pul- monary hypertension, interstitial fibrosis or asthma), 22.6% with congestive heart failure, 7.4% with peripheral vascular disease (PVD) and 12.5% with cerebrovascular disease (CVD). Diabetes mellitus was identified in 18.8% of the geriatric IBD patients and 9.4% had diabetes with end-organ damage. History of stroke was seen in 12.5% of geriatric IBD patients and moderate to severe renal disease was seen in 11.5% of patients. Rheumatologic diseases were identi- fied in 10.2% of the geriatric IBD population and 2.5% suffered from dementia. Gastrointestinal diseases in addi- tion to IBD were also identified, which included 17.8% with peptic ulcer disease/history of GI bleeding, 1.5% with mild liver disease and 10.7% with moderate to severe hepatic dysfunction. Human immunodeficiency viral infection was identified in 0.5% of the geriatric IBD patient population.

We calculated a comorbidity index for the geriatric IBD patients, which showed male patients with 3.2 ± 3.0 ill- nesses and females with 2.7 ± 2.8 illnesses ($p = 0.12$).

Age at diagnosis of IBD was not related to comorbid index (diagnosed B64 years of age was 2.93 ± 2.90 and those diagnosed C65 was 2.96 ± 2.96, $p = 0.91$).

There was a small positive correlation between duration of CD and increased comorbidity (Charlson comorbidity

index $r = 0.028$, p \ 0.005). Similar findings were not appreciated in elderly UC patients ($r = 0.097$, $p = 0.36$).

Discussion

Little is known about IBD in the elderly population, as medication trials did not include this population. Recog- nizing current prescribing patterns and natural disease history in this population is needed as a first step in pre- venting complications and improving quality of care delivered to older individuals with IBD. We characterized patterns of phenotypic presentation, treatment, polyphar- macy, nutritional status, comorbidity, outcomes and mor- tality in a cohort of geriatric IBD patients followed in a large tertiary referral center. Our study defined several important parameters regarding the geriatric IBD popula- tion at the present time. There were a disproportionately small number of geriatric IBD patients, suggesting that the diagnosis occurred rarely in past decades given the dura- tion of disease in our cohort. Phenotypic variation was seen between patients with earlier diagnosis of CD in compar- ison to those with later diagnosis. Fistulizing/penetrating

disease was frequent in patients diagnosed with CD at a younger age. Younger age at diagnosis of CD (B64) was also associated with greater prevalence of small bowel

surgeries compared with those diagnosed after age 65. Maintenance therapy with 5ASA agents was most fre- quently used, but a subgroup of geriatric IBD patients were receiving both oral and topical steroids on a long-term basis. Immunomodulator and biologic use was rare in the geriatric IBD population.

There was correlation between age at diagnosis of IBD and prescribing of steroids.

Nutritional deficiencies in vitamin B12, vitamin D and iron were identified in a subgroup of geriatric IBD patients and it correlated with the duration of disease in CD. Major polypharmacy, with five or more medications being used on a regular basis was seen in a majority of the geriatric IBD patients. Comorbidity was seen in the geriatric IBD patients, with cardiovascular disease, pulmonary disease and diabetes mellitus being most frequently encountered.

Life expectancy in the United States has been steadily increasing. The average life expectancy for Americans in the year 2005 was 77.8 years, and this has been projected to rise to 79.5 years of age by 2020 [17]. This aging of the

U.S. population is expected to carry important ramifica- tions regarding society's ability to care for individuals as they acquire health problems, but also carries implications regarding the population of chronically ill individuals, including patients with IBD, as they age. Although CD and UC are typically considered diseases of the young, with peak incidences in the second to fourth decades of life [18, 19], it is generally accepted that there is a bimodal age distribution with a second smaller peak in incidence in the sixth to eighth decade [18, 19]. At the present time it is estimated that 10–15% of cases of IBD are diagnosed in

patients aged 60 years or older [18, 20]. Of these, 65% present in their 60s, 25% in their 70s, and 10% in their 80s [21].

The clinical presentation of geriatric IBD may also be different compared to the general IBD population. IBD in older patients may involve different segments of the ali- mentary tract, with a larger percentage of patients dem- onstrating colitis due to the higher numbers of geriatric patients with UC. Likewise, there are limited data at this time regarding the impact of geriatric age on response to therapy. The recent study by Ananthakrishnan et al. [2] suggested that geriatric IBD patients demonstrated higher rates of complications and increased mortality compared to younger individuals. Data from the surgical literature have shown that elderly IBD patients have an increased rate of postoperative complications along with an increased length of hospital stay and increased operating room time. This deleterious effect of age persisted when adjusted for comorbidity and immunosuppressive therapy [4]. Geriatric IBD patients have also demonstrated hypercoagulability and a higher incidence of thromboembolism, particularly in the inpatient setting, where 3% of admissions were com- plicated by thrombosis [22].

There has been limited research regarding the specific clinical factors which contribute to poor outcome in geri- atric IBD. Several studies focused on geriatric IBD have used administrative datasets, which rely heavily on analysis of diagnosis/procedure codes (i.e. ICD-9 codes) associated with clinical data. This approach can give important overall information, but may be limited in its ability to ascertain specific patient care details and is inherently limited due to these constraints [23]. Our study sought to provide addi- tional information regarding the care of geriatric IBD patients by reviewing clinical information (i.e. retrospec- tive chart review) to determine treatment patterns and details

regarding specific clinical issues that will not be captured by ICD-9 codes. The ability to ascertain clinical details from patient records has been made more difficult at the present time due to restrictions imposed by HIPAA privacy guidelines which were implemented in 2003. We were able to overcome this hurdle and provide details regarding specific clinical information in the geriatric IBD patient cohort through collaboration with bioinformatics experts at our institution. The development of de-identifi- cation software at the University of Pittsburgh Department of Biomedical Informatics which selectively removes protected health information has allowed clinical investi- gation using de-identified data from the EMR to be rou- tinely available for research.

Our study identified a relatively small number of geri- atric IBD patients. This was remarkable, as there was a sizeable geriatric population in both Allegheny county (16.8%), home to the city of Pittsburgh and the main

UPMC hospitals, as well as the state of Pennsylvania (15.4%) in the year 2009 [24].

One of the most important findings in our study was the characterization of maintenance treatment used by the geriatric IBD cohort. High rate of sulfasalazine may be related to the lower cost of this generic agent, as typically the elderly have a limited and fixed income, cost may be playing a role in their selection of medications. Also we noted that there was only one patient on budesonide (more expensive medication than prednisone). Patient's health insurance may have driven the prescribing habits of the physicians, but since our database was a de-identified dataset, we did not have information about patient's health insurance (i.e. percent of patients who were on medicare only vs. private insurance vs. Medicaid, etc.).

At the present time, there has been an upsurge in the use of immunomodulator and biologic therapy for the mainte- nance of remission in patients with IBD. Remarkably, in our geriatric IBD cohort, only a minority of patients (\10% of the total) were receiving these medications. The small percentage of patients on biologics may not be surprising given the FDA approval dates for the major biologics.

Prior literature suggests that tolerability of these agents in the elderly population has been overall good and there are no specific recommendations to restrict use of these drugs in elderly patients at this time. IBD medications including aminosalicylates and infliximab have been found to be safe and effective for patients older than 65 [25, 26]. Also, azathioprine and 6-MP are generally well tolerated by individuals up to age 70 [27, 28], but we did find two patients with liver abscess as a complication of azathio- prine. In marked contrast to the low use of immunomod- ulator/biologic agents in our cohort of geriatric IBD patients, we identified high rates of long-term corticoste- roid use ([6 months duration). We also identified that

patients with new diagnosis of IBD C65 are treated with

higher dose and frequency of steroids than patients who had the diagnosis when they were younger. Again, there is literature which has demonstrated that geriatric patients are at a higher risk to develop corticosteroid complications compared with younger individuals. Corticosteroids may exacerbate conditions such as congestive heart failure,

hypertension, osteoporosis, cataracts or glaucoma, diabe- tes, psychosis or depression, infections and electrolyte abnormalities [25]. We noted a significant number of patients treated with prednisone with diagnosis of CAD and CHF. A possible explanation for higher use of steroids in the elderly population is that elderly patients might choose treatment regimens which require less stringent blood monitoring when compared with immunomodulators. The patterns of long-term systemic corticosteroid use suggest that increased use of immunomodulator agents could be

considered a potential steroid sparing strategy in these geriatric CD individuals.

Polypharmacy with prescription and over the counter medications is common in elderly. One study showed nearly 1 in 25 geriatric individuals were at potential risk for a major drug–drug interaction [29]. Data is limited regarding polypharmacy in the geriatric IBD population at the present time. We noted underutilization of immune modulators and higher use of long-term steroids in the elderly IBD patient population. It appears that elderly patients with IBD are undertreated especially with immune modulators, which may be due to the fear of side effects in the fragile elderly cohort.

Protein Energy Malnutrition (PEM) occurs in 20–85% of IBD patients [11, 30]. Although PEM is most frequent in active hospitalized IBD patients, nutritional and functional deficits may persist in inactive outpatients, especially in those with long-standing IBD requiring continuous steroid therapy [31]. There is limited data comparing the duration of IBD with nutritional deficiencies in elderly patients. We found that the duration of CD correlates positively with the vitamin B12, iron and vitamin D deficiency. It is possible that patients with longer duration of CD may have dietary aversions and have more surgeries involving their bowel, leading to nutritional deficiencies. We did not find similar findings in our UC cohort. Our data suggest that geriatric patients with longer duration of CD need to be more clo- sely monitored for nutritional deficiencies.

Ours is a retrospective observational study utilizing patient charts and a sophisticated de-identified EMR soft- ware system. As such it has the limitations inherent to an analysis of this type. Paper charts were not incorporated in our dataset and this made complete lifetime treatment histories unavailable for the majority of our patients. Although this prevented us from providing a definitive natural history of geriatric IBD, we were able to provide information on the most recent treatments available for our patients. Also, it is possible that nutritional deficiencies could have been measures only in the higher risk popula- tion. We found lower prevalence of iron and vitamin D deficiency in our study population, which could be related to some of the patients being excluded from our data analysis, as complete nutritional data was available in those patients. Although our study was not a case control, we believe that in literature, data about patterns of IBD-spe- cific measures (anti-TNF, mesalamine, etc.) and non-IBD measures (polypharmacy, lab-values, etc.) in elderly is practically unknown and we have tried to put historical values for comparison (where available) in our manuscript. Our study suggests that elderly IBD patients may not be benefitting from optimal immunomodulator maintenance regimens, as a significant cohort were receiving chronic

corticosteroids. Prospective studies characterizing natural history of geriatric IBD, performance of immunomodulator/biologic agents and the effects of comorbid illness on IBD natural history are warranted to define optimal treatment regimens and plan for future allocation of health care resources in the aging population.

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Conflict of interest None.

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METABOLIC AND STEAT O HE PATITIS

Hepatic steatosis in diabetic patients does not predict adverse liver-related or cardiovascular outcomes

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Keywords

diabetes – NAFLD – NASH – steatosis

Abbreviations

CIMT, carotid intimal-medial thickness; CT, computed tomography; MR, magnetic resonance; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; PACS, picture archiving communication system; UPMC, University of Pittsburgh Medical Center.

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Abstract

Background & Aims: Steatosis is a defining feature of nonalcoholic fatty liver disease (NAFLD). However, evidence that severity of steatosis can predict adverse outcomes in NAFLD or nonalcoholic steatohepatitis (NASH) is lack- ing. The aim of this study was to determine whether steatosis assessed by computed tomography (CT) imaging predicts adverse outcomes in diabetic patients at risk for NAFLD/NASH. Methods: We studied deaths, liver- related and cardiovascular adverse outcomes in a 5-year retrospective obser- vational cohort of 2343 type 2 diabetic patients in a large care network who had noncontrast CT imaging for clinical indications. We measured steatosis by subtraction of spleen from liver attenuation, a method that showed low sensitivity (0.417) and high specificity (0.882) compared with histopathologi-

cal scoring. We evaluated outcomes prediction using multivariate Cox proportional hazards modelling of steatosis both as a categorical (≥30%) and continuous variable. Results: Steatosis ≥30% was present in 233 (9.9%) of

the cohort at baseline. Over 5 years, there were 372 total deaths, 18 liver-related and 99 cardiovascular deaths, 48 liver transplants, 51 occur- rences of hepatic encephalopathy, 41 hepatocellular carcinomas, 653 myocar- dial infarctions, 66 strokes, 180 occurrences of angina, 735 occurrences of arrhythmia and 772 occurrences of congestive heart failure. Steatosis had no predictive value for any adverse outcome. Patients with steatosis averaged 8 years younger than those without it. Age had a strong covariate influence on occurrence of total deaths, cardiovascular deaths, myocardial infarctions, arrhythmias and congestive heart failure. Conclusion: Although steatosis on imaging is often the abnormality that triggers diagnosis and assessment of NAFLD/NASH, it lacks predictive value for adverse clinical outcomes.

Hepatic steatosis on abdominal imaging is frequently the first indicator of the presence of nonalcoholic fatty liver disease (NAFLD). Its extent or severity, like that of many other presenting clinical abnormalities, tends to drive the level of effort expended on defining and man- aging the clinical problem. In NAFLD, however, it is not clear whether the severity of hepatic steatosis has value in predicting outcomes or guiding patient care.

Steatosis as an imaging or histopathological finding defines NAFLD; examination of a liver biopsy is needed to assess the presence of its progressive form, nonalco- holic steatohepatitis (NASH) (1). Adverse cardiovascu- lar events are the leading cause of death and morbidity in patients with NAFLD, who frequently have type 2 diabetes and the other cardiovascular components of

the metabolic syndrome (2). Hepatic steatosis on ultra- sonography was reported to be independently associated with cardiovascular disease, but not cardiovascular mortality in a population survey (3). Hepatic steatosis was correlated with carotid intimal-medial thickness (CIMT), a marker of cardiovascular risk, in a report from China (4). Steatosis on ultrasonography was asso- ciated with an increased Framingham cardiovascular

risk score in two reports from Korea (5, 6). Japanese diabetic patients aged ≥65 with hepatic steatosis on

ultrasonography had an increased risk of macroangiopa- thy and coronary heart disease, but younger patients did not (7). In a US community-based cohort study of 337 type 2 diabetic patients, Adams et al. found that overall mortality was associated with a diagnosis of NAFLD in

116 patients as assessed by ultrasonography or liver biopsy showing steatosis, with a hazard ratio of 2.2, and that NAFLD was associated with significantly higher mortality caused by liver disease and malignancy (8).

On the other hand, a cohort of 170 Danish patients with NAFLD and simple steatosis on biopsy followed up for 15 years had no greater mortality or progression to cirrhosis than that for age and gender-matched controls from a national patient registry (9). Reports from Italy and Turkey showed no relationship of hepatic steatosis on ultrasonography with CIMT (10, 11), in agreement with a study of French diabetic patients in whom hepa- tic steatosis measured by magnetic resonance (MR) spectroscopy was not correlated with CIMT (12). We determined the occurrence of significant hepatic steato-

sis of ≥30%, as shown with high reported specificity by

unenhanced abdominal computed tomography (CT) imaging, in a cohort that included all patients with type 2 diabetes in an integrated delivery system, who had such imaging over a 2-year baseline period for any clini-

cal indication. We studied whether steatosis of ≥30%

could predict occurrence of adverse liver-related and cardiovascular outcomes over 5 years in these patients known to be at risk for NAFLD.

Methods

Patient cohort

We extracted data from the electronic health records of all 4721 patients seen in the primary care and specialty clinics of a large integrated delivery network, the University of Pittsburgh Medical Center (UPMC), who

had an ICD9 coded diagnosis of Type 2 diabetes, who were ≥18 years of age and who had a noncontrast

abdominal CT scan between January 1, 2002 and December 31, 2003 for any clinical indication. Scans were performed for a broad range of indications in out- patients and inpatients, most commonly including abdominal distress, suspected nephrolithiasis/uretero- lithiasis, suspected steatosis and concern for aortic aneu- rysm. We used the search and aggregation functionality of UPMC's Medical Archival Retrieval System as described for other retrospective outcomes studies using electronic records (13). Clinical data and CT images were de-identified by an honest broker and images were stored on a research server. This study was designated exempt by the University of Pittsburgh Institutional Review Board.

As shown in Fig. 1, we excluded patients with ICD9 diagnostic codes indicating potential confounding causes of hepatic steatosis or liver diseases other than NAFLD, including alcohol abuse, alcoholic liver disease,

chronic hepatitis B and C, autoimmune hepatitis, biliary cirrhosis, Wilson disease, hemochromatosis, a-1 anti- trypsin deficiency or a prior liver transplant. Also excluded were patients with records showing positive hepatitis B or C serology without ICD9 coding, baseline liver malignancy either coded or seen on imaging, records where images were not retrievable from the Pic-

ture Archiving Communication System or not evaluable for steatosis because of an absent spleen, or where the only information in the record was an imaging report. The remaining 2343 patients who formed our observa- tional cohort had an evaluable baseline CT scan and at least one clinical note. We evaluated clinical information

Fig. 1. Definition of a retrospective observational cohort of 2324 patients with a diagnosis of Type 2 diabetes and a noncontrast abdominal computed tomography scan performed in 2002 or 2003.

and events present at baseline and recorded through the end of 2008, 5 years after the end of the 2002–2003 baseline period.

Hepatic steatosis measurement

We evaluated unenhanced CT images for steatosis as shown in Fig. 2. For each patient, attenuation (Houns- field units) of liver and spleen was calculated as the mean value of three regions of interest positioned at supraportal, portal and infraportal levels. The difference between mean liver and spleen attenuation (L - S) was

then calculated. We considered an (L - S) value of -10 or less to indicate the presence of ≥30% hepatic steato-

sis, a measurement reported to have 100% specificity (14).

We evaluated concordance between CT and histo- pathological assessments of steatosis in 41 liver biopsy specimens by scoring steatosis as described by Kleiner et al. (1) and determining the relationship of the histo- pathological steatosis scores with CT steatosis measure- ments. We assessed stability and consistency of the (L - S) measurement over time in 81 patients who had two scans performed between 1 and 12 months apart.

Outcomes analysis

We recorded liver-related deaths, liver transplantation, hepatic encephalopathy and hepatocellular carcinoma as adverse liver-related outcomes, and cardiovascular deaths, myocardial infarctions, strokes, angina, arrhyth- mias and congestive heart failure as adverse cardiovas- cular outcomes. Liver-related, cardiovascular and total

Fig. 2. Measurement of hepatic steatosis using a noncontrast abdominal computed tomography scan. Attenuation was averaged for three regions in the liver and the spleen at supraportal, portal and infraportal levels. Averaged attenuation for the spleen was sub- tracted from that for the liver to give a value of L - S. The value of L - S for the illustrated scan is -69.6 Hounsfield units, indicating severe hepatic steatosis.

deaths were determined by review of clinical death summaries. Nonfatal adverse outcomes were assessed by their corresponding ICD9 codes. We evaluated the accu- racy of ICD9 coding of adverse outcomes by review of the full text of 100 electronic records.

Data were analysed using the R statistical package, version 2.15.2012-10-21 (15). Baseline characteristics and outcomes were compared for patients based on

steatosis classification of ≥30% vs. <30%. Continuous

variables were checked for normality and non-normal values were presented as medians with interquartile ranges and compared with Wilcoxon-rank sum testing. Continuous normal values were compared with t-tests except where the cell values were <5, when Fisher's exact test was used. Categorical values were compared using chi-square testing. A Kaplan–Meier curve was used to assess differences in survival times by steatosis category. Multivariate Cox proportional hazards models were created to assess the effects of steatosis on outcomes using first steatosis as a categorical variable (<30% vs.

≥30%) and then validating the findings by using L - S

as a continuous measure of steatosis. L - S was scaled by the statistical programme prior to entry into the models. For specific causes of death including liver- and cardiovascular-related deaths, competing risk models were created using death from other causes as a compet- ing risk. All models were checked for multicollinearity. Covariates were entered into the model to account for baseline disease and known confounders and those vari- ables of relevance in the univariate analysis. Owing to the high frequency of missing BMIs and lab values from the data set we were unable to control for these factors.

Results

Baseline patient characteristics

Baseline characteristics of the patients are shown in Table 1. Steatosis of ≥30% was present in 233 of the cohort of 2343 or 9.9%. The patients with ≥30% steato-

sis were significantly younger by an average of 8 years, and had significantly higher baseline BMI, LDL, triglyc- eride, AST and haemoglobin A1C levels compared with values for the 2110 patients with <30% steatosis. A base- line ICD9-coded diagnosis of NAFLD was significantly

more frequent in those with ≥30% steatosis. A history of

baseline myocardial infarction, arrhythmia and conges- tive heart failure was significantly more frequent in the patients with <30% steatosis. Baseline cirrhosis, hepatic encephalopathy, stroke and angina were not signifi- cantly different between the patient groups.

Steatosis and adverse outcomes

Deaths and adverse outcomes during this study period are shown in Table 2. There was a significantly greater occurrence of total deaths, arrhythmias and congestive heart failure in patients with <30% steatosis, and a

Table 1. Baseline characteristics

<30%

steatosis,

≥30%

steatosis,

Full Cox proportional hazards models for 372 total

deaths, 18 liver-related deaths, and 99 cardiovascular deaths are shown in Table 3, both with ≥30% steatosis as

Variable

N = 2110

N = 233 P

a categorical variable and with steatosis as a continuous

Age 66.6 ± 15.1 58.1 ± 13.7 <0.001

Female gender 1131 (54) 134 (58) 0.29

Non-Caucasian	337 (16)	27 (12)	0.10
BMI	30.8 ± 7.5	36.7 ± 8.5	<0.001
LDL	92 (70, 119)	105 (74, 133)	0.01
TG	141 (94, 202)	206 (147, 294)	<0.001
AST	22 (17, 34)	26 (18, 39)	<0.001
A1C	7.2 ± 1.9	7.7 ± 2.1	0.049
Baseline ICD9 Dx			
Cirrhosis	104 (5)	10 (4)	0.78
NAFLD	58 (3)	20 (9)	<0.001
Encephalopathy	12 (1)	1 (0.4)	0.75
MI	467 (22)	29 (12)	<0.001
Stroke	109 (5)	8 (3)	0.32
Angina	212 (10)	15 (6)	0.10
Arrhythmia	631 (30)	35 (15)	<0.001
CHF	639 (30)	23 (10)	<0.001

Continuous variables are shown as mean ± SD, or median (IQR) for non-normal variables, and categorical variables are shown as N (column

%). P values shown are from t-tests for normal continuous variables,

Wilcoxon-rank sum tests for non-normal continuous variables, and Chi- square tests for categorical variables, with Fisher's Exact Test for those categorical variables with low cell counts. Baseline BMI was recorded in 36%, LDL in 63%, triglycerides in 70%, AST in 94%, and haemoglobin A1C in 29% of the cohort.

Table 2. Adverse outcomes by steatosis category

variable (L - S). Covariates for all the models were cho- sen a priori using known risk factors for each outcome as well as differences on univariate testing in this data set. However, for models of outcomes that were rare (such

as liver-related death) only the most important potential confounders could be included and a larger sample size would have been needed to adequately evaluate the other variables. Age had consistently strong predictive values

for total and cardiovascular deaths in both the categori- cal (< or ≥30%) and continuous (L - S) analyses, as did

baseline cirrhosis for total and liver-related deaths, base- line myocardial infarction and congestive heart failure for cardiovascular deaths, and baseline congestive heart failure for total deaths. When modelled as a categorical

variable, steatosis ≥30% was associated with decreased

risk of total deaths (HR 0.41); however, when modelled as a continuous variable the same effect was not observed. L - S increases as steatosis decreases, so that the significant hazard ratio of 1.05 for liver-related deaths modelled with L - S indicates greater hazard of liver-related death with lesser steatosis.

As shown in Table 4, steatosis was not associated with any nonfatal adverse liver-related or cardiovascular outcome whether modelled as a categorical or continu- ous variable. Age was associated with myocardial infarc- tion, congestive heart failure and arrhythmia. Baseline cirrhosis was associated with all adverse liver outcomes, and each baseline liver-related and cardiovascular con-

Adverse outcome

Total sample,

N = 2343

<30%

steatosis,

N = 2110

≥30%

steatosis,

N = 233 P

dition predicted its own subsequent adverse outcome. Prior myocardial infarction was associated with conges- tive heart failure and angina, and prior congestive heart

Death in the study

372 (41) 359 (17) 13 (6) <0.001

failure was associated with arrhythmias. All outcomes associations were consistent between categorical (≥30%)

and continuous (L - S) analyses.

Cardiovascular outcomes

MI 653 (28)

Stroke 66 (3)

Angina 180 (8)

Arrhythmia 735 (31)

CHF 772 (33)

Data are presented as N (%). P values were derived from Chi-square tests unless the cell value was <5, in which case Fisher's Exact Test was used.

nonsignificant trend towards greater occurrence of myocardial infarction in that group as well. A Kaplan– Meier survival curve, shown in Fig. 3, illustrates the dif- ferences in survival over time by steatosis category.

Concordance of CT steatosis measurement with histopathology, stability of CT measurement over time and assessment of ICD9 coding of records

CT measurement of ≥30% steatosis is shown in Table 5 for 41 patients, in which the CT measurements were assessed against the standard of histopathological scor- ing of steatosis as described by Kleiner et al. (1). We found low sensitivity, 0.417, and high specificity, 0.882, for the CT measurement. For ease of analysis, we equa- ted histopathological steatosis scores of 2 or 3 for this

assessment, defined as ≥25% steatosis, to CT measure- ments of ≥30%.

Attenuation measurements for 81 paired CT scans performed between 1 and 12 months apart were stable over time as shown by positive correlation (r = 0.68) (data not shown).

A full text sample of 100 electronic records contained an average of 80.5 clinical reports including outpatient

Fig. 3. Kaplan–Meier plot of full Cox proportional hazards modelling of patients remaining at risk for adverse clinical outcomes after a base- line abdominal computed tomography scan showing steatosis ≥30% vs. <30%.

Table 3. Full Cox proportional hazards models for death*

Model	Variable	HR	95% CI	P	Variable	HR	95% CI	P
All deaths	≥30% steatosis	0.41	0.23, 0.71	0.002	L - S	1.07	0.95, 1.20	0.28
	Age	1.03	1.02, 1.04	<0.001	Age	1.03	1.02, 1.04	<0.001
	Female	1.00	0.82, 1.24	0.97	Female	0.99	0.80, 1.22	0.92
	Race	1.30	0.99, 1.71	0.06	Race	1.31	0.99, 1.72	0.06
	Cirrhosis	2.09	1.37, 3.18	<0.001	Cirrhosis	2.14	1.40, 3.26	<0.001
	MI	1.15	0.91, 1.46	0.24	MI	1.15	0.91, 1.46	0.25
	CHF	2.46	1.97, 3.08	<0.001	CHF	2.54	2.03, 3.17	<0.001
Liver-related deaths	≥30% steatosis	0.42	0.05, 3.35	0.42	L - S	1.05	1.00, 1.11	0.04†
	Age	1.01	0.97, 1.05	0.72	Age	1.01	0.97, 1.04	0.71
	Cirrhosis	80.5	25.4, 255.2	<0.001	Cirrhosis	94.20	30.4, 292.0	<0.001
Cardiovascular deaths	≥30% steatosis	0.30	0.07, 1.23	0.09	L - S	1.01	0.99, 1.02	0.52
	Age	1.05	1.03, 1.08	<0.001	Age	1.06	1.03, 1.08	<0.001
	Female	1.15	0.77, 1.72	0.49	Female	1.13	0.76, 1.69	0.54
	Cirrhosis	1.13	0.35, 3.65	0.84	Cirrhosis	1.16	0.36, 3.76	0.80
	MI	1.56	1.01, 2.40	0.04	MI	1.56	1.01, 2.40	0.045
	CHF	2.85	1.80, 4.51	<0.001	CHF	2.95	1.86, 4.68	<0.001

*Death from other causes was considered as a competing risk in the liver-related and cardiovascular death models Comorbidities are defined as prior to the computed tomography scan.

†L - S increases as steatosis decreases. A HR >1 for L - S indicates greater hazard with lesser steatosis.

and inpatient notes and summaries (range 2–565, SD = 99). The average file size was 0.41 MB (range 0.014–3.90, SD = 0.61). A text review showed that 277, or 85.8%, of the 323 recorded ICD9 codes for nonfatal liver-related and cardiovascular adverse outcomes were

substantiated by narrative text. Inaccurate ICD9 coding included 45 unsubstantiated outcomes and 6 that were missed and not coded. Narrative information suggesting presence of the potentially confounding liver diseases listed earlier was not present in the reviewed records.

Table 4. Full Cox proportional hazards models for nonfatal adverse outcomes

Outcome	Variable	HR	95% CI	P	Variable	HR	95% CI	P
Transplant	≥30% steatosis	0.63	0.22, 1.76	0.38	L - S	1.00	0.97, 1.03	0.94
	Age	0.99	0.97, 0.998	0.03	Age	0.99	0.97, 0.999	0.03
	Female	0.55	0.31, 0.98	0.04	Female	0.55	0.31, 0.98	0.04
	Race	0.82	0.29, 2.34	0.72	Race	0.84	0.30, 2.39	0.74
	Cirrhosis	18.15	10.00, 32.93	<0.001	Cirrhosis	18.26	10.08, 32.09	<0.001
HCC	≥30% steatosis	0.42	0.10, 1.76	0.24	L - S	1.01	0.98, 1.04	0.11
	Age	1.01	0.99, 1.04	0.29	Age	1.01	0.99, 1.04	0.27
	Female	0.73	0.39, 1.34	0.30	Female	0.72	0.39, 1.32	0.29
	Race	0.54	0.17, 1.76	0.31	Race	0.54	0.17, 1.77	0.31
	Cirrhosis	6.11	2.87, 13.00	<0.001	Cirrhosis	6.26	2.94, 13.35	<0.001
PSE	≥30% steatosis	0.89	0.38, 2.11	0.79	L - S	1.01	0.98, 1.04	0.39
	Age	1.00	0.99, 1.02	0.74	Age	1.00	0.99, 1.02	0.77
	Female	1.40	0.78, 2.50	0.26	Female	1.41	0.79, 2.53	0.24
	Race	0.81	0.29, 2.23	0.68	Race	0.79	0.29, 2.18	0.65
	Cirrhosis	39.14	21.35, 71.76	<0.001	Cirrhosis	40.20	21.81, 74.09	<0.001
	Prior PSE	5.64	1.74, 18.19	<0.001	Prior PSE	5.82	1.80, 18.78	<0.001

MI	≥30% steatosis	0.77	0.58, 1.02	0.07	L - S	1.00	1.00, 1.01	0.30	
	Age	1.02	1.02, 1.03	<0.001	Age	1.02	1.02, 1.03	<0.001	
	Female	0.91	0.78, 1.06	0.24	Female	0.94	0.78, 1.06	0.21	
	Race	0.96	0.76, 1.21	0.71	Race	0.96	0.76, 1.21	0.71	
	Cirrhosis	1.10	0.73, 1.66	0.65	Cirrhosis	1.12	0.74, 1.68	0.60	
	Prior MI	3.94	3.35, 4.64	<0.001	Prior MI	3.95	3.36, 4.65	<0.001	
CHF	≥30% steatosis	0.87	0.65, 1.16	0.33	L - S	1.00	0.99, 1.01	0.87	
	Age	1.03	1.02, 1.03	<0.001	Age	1.03	1.02, 1.03	<0.001	
	Female	0.98	0.85, 1.13	0.81	Female	0.98	0.85, 1.13	0.78	
	Race	0.92	0.75, 1.13	0.44	Race	0.92	0.75, 1.14	0.46	
	Cirrhosis	1.01	0.70, 1.46	0.97	Cirrhosis	1.01	0.70, 1.47	0.94	
	Prior CHF	4.95	4.22, 5.80	<0.001	Prior CHF	4.99	4.25, 5.85	<0.001	
	Prior MI	1.18	1.01, 1.39	0.04	Prior MI	1.18	1.01, 1.39	0.04	
Angina	≥30% steatosis	0.72	0.42, 1.22	0.22	L - S	1.01	0.99, 1.02	0.39	
	Age	1.01	1.00, 1.02	0.09	Age	1.01	1.00, 1.02	0.09	
	Female	1.13	0.84, 1.52	0.42	Female	1.12	0.83, 1.51	0.46	
	Race	1.14	0.77, 1.70	0.51	Race	1.14	0.76, 1.69	0.53	
	Cirrhosis	0.30	0.07, 1.23	0.09	Cirrhosis	0.31	0.08, 1.25	0.10	
	Prior CHF	1.11	0.78, 1.57	0.57	Prior CHF	1.12	0.79, 1.58	0.54	
	Prior MI	2.00	1.41, 2.84	<0.001	Prior MI	2.00	1.41, 2.84	<0.001	
	Prior Angina	3.15	2.22, 4.48	<0.001	Prior Angina	3.15	2.22, 4.47	<0.001	
Arrhythmia	≥30% steatosis	0.80	0.60, 1.07	0.14	L - S	1.00	1.00, 1.01	0.56	
	Age	1.03	1.02, 1.04	<0.001	Age	1.03	1.03, 1.04	<0.001	
	Female	0.82	0.71, 0.95	0.01	Female	0.82	0.71, 0.95	0.01	
	Race	1.01	0.82, 1.25	0.91	Race	1.01	0.82, 1.24	0.91	

	Cirrhosis	1.36	0.95, 1.95	0.09	Cirrhosis	1.37	0.96, 1.97	0.08	
	Prior MI	1.09	0.92, 1.29	0.32	Prior MI	1.09	0.92, 1.29	0.33	
	Prior CHF	1.81	1.54, 2.14	<0.001	Prior CHF	1.83	1.55, 2.16	<0.001	
	Prior arrhythmia	2.85	2.43, 3.35	<0.001	Prior arrhythmia	2.86	2.44, 3.36	<0.001	
Stroke	≥30% steatosis	0.69	0.28, 1.75	0.44	L - S	1.00	0.98, 1.02	0.92	
	Age	1.02	1.00, 1.04	0.10	Age	1.02	1.00, 1.04	0.09	
	Female	1.34	0.81, 2.21	0.25	Female	1.35	0.82, 2.23	0.24	
	Race	0.98	0.51, 1.87	0.95	Race	1.01	0.53, 1.92	0.98	
	Prior MI	1.23	0.72, 2.11	0.45	Prior MI	1.24	0.72, 2.13	0.43	
	Prior stroke	13.64	8.12, 22.90	<0.001	Prior stroke	13.59	8.09, 22.82	<0.001	

Discussion

Steatosis is a defining metabolic and histopathological

hallmark of NAFLD and NASH. Our data show that a finding of ≥30% hepatic steatosis in diabetic patients

with a clinical indication for abdominal imaging lacked predictive value over 5 years for any adverse liver-

related or cardiovascular outcome and that modelling of L - S as a continuous variable produced the same result. On the other hand, patient age was a strong predictor of total and cardiovascular deaths and most cardiovascular adverse events.

Adams et al. found significant associations between total and liver-related deaths and hepatic steatosis in a

Table 5. Sensitivity and specificity of computed tomography (CT)

steatosis measurements compared with biopsy scores

progressive or advanced disease. A strong point of our study is its use of a CT imaging analysis method with

Steatosis ≥30% by CT scan		
Steatosis <30% by CT scan		

reported 100% specificity for identifying hepatic steato- sis of ≥30% (14). We found that the measurement had comparable specificity, 88%, when assessing our steato-

Steatosis 0 or 1 on biopsy	2	15
Steatosis 2 or 3 on biopsy	10	14

CT measurement of steatosis ≥30% had a sensitivity of 0.417, specific- ity of 0.882, positive predictive value of 0.833 and negative predictive value of 0.517, as compared with a histopathological steatosis score of 2 or 3 that estimates 25% or greater steatosis (1).

community-based cohort study of patients with type 2 diabetes that we did not observe in our study cohort (8). Potentially important differences between that report and this study include its community-based rather than event-driven cohort composition and its 10-year vs. 5-year period of observation.

Our patient sample was not chosen to be representa- tive of the full adult diabetic population, but did appear to fairly represent diabetic patients at risk for NAFLD who require imaging for any reason, and in whom a finding of steatosis regularly triggers consideration of its prognostic significance. Lack of recorded evidence of confounding liver diseases does not assure their absence from the cohort, especially because these conditions were not systematically sought in the context of routine patient visits unless a clinical manifestation of liver disease, as shown in Table 2 for 158 patients

with an adverse liver-related outcome, became evident. On bal- ance, however, NAFLD appears to have been the likely dominant cause of the adverse liver-related outcomes that we observed, as suggested by our full text review of a 100-patient record sample. The predominance of adverse cardiovascular compared with liver-related out- comes is consistent with that reported for diabetic patients with NAFLD (2).

A biologically plausible explanation for our finding of the lack of predictive value of steatosis in our cohort is the younger average age of patients with steatosis com- pared with the older age of those without it, in whom adverse outcomes were concentrated. The disappearance over time of steatosis in many patients with age, as NA- FLD advances to NASH and end stage cirrhosis, is well known (16, 17). Those reports and our observations suggest that it would be relevant to assess the signifi- cance of changes in steatosis as NAFLD and NASH evolve over a prolonged period.

In clinical context, our data support recommenda- tions that an imaging finding of significant hepatic stea- tosis should prompt consideration of alternative causes of steatosis and of the potential value of histopathologi- cal assessment to define NASH to determine the impor- tance of treatment efforts in an individual patient (18). Conversely, the absence of marked steatosis on imaging, especially in an older patient with risk factors for NAFLD/NASH, does not exclude the presence of

sis measurements against biopsy steatosis scoring as described by Kleiner et al. (1). Ultrasonography is more widely available than CT or MR spectroscopy, and a recent meta-analysis concluded that its diagnostic accu- racy for steatosis was equivalent to that of CT or MR (19). However, two recent reports showed that severe obesity, highly prevalent in NAFLD, degrades the accu- racy of ultrasonography for assessing steatosis, with specificity of only 55% for severely obese adolescents

(20) and 68% for patients before bariatric surgery (21). Our finding of 9.9% steatosis ≥30% in our patients is in

the lower range of that reported for steatosis in an adult diabetic population, and likely reflects the stringency of a method that targeted high specificity (22). Different imaging methods and cut-offs increase sensitivity at the cost of specificity, so that application of various pub- lished imaging criteria in a single patient cohort yielded a steatosis prevalence ranging from 6 to 45% (23).

With respect to hepatic steatosis and cardiovascular risk, it appears unlikely that variation in imaging meth- ods can account for the discrepant results of studies that reported an association between hepatic steatosis and cardiovascular risk markers (4–7) and those that did not (10–12). Our data showing the importance of age rather than steatosis for adverse outcomes may be relevant in this respect, in the light of a report from Japan that the association of hepatic steatosis with cardiovascular risk was age specific (7).

To conclude, there is strong published evidence that hepatic steatosis detected on imaging merits clinical consideration of NASH and the cardiovascular risks of the metabolic syndrome. Our data show, however, that severe steatosis in our patients lacked predictive value for adverse liver-related and cardiovascular outcomes over a 5-year period. We hypothesize that loss of steato- sis as NASH progresses and worsens with time and advancing age may largely account for our findings.

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Association Between Telephone Activity and Features of Patients With Inflammatory Bowel Disease

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BACKGROUND & AIMS: Telephone communication is common between healthcare providers and patients with inflammatory bowel disease (IBD). We analyzed telephone activity at an IBD care center to identify disease and patient characteristics associated with high levels of telephone activity and determine if call volume could identify individuals at risk for future visits to the emergency department (ED) or hospitalization.

METHODS: We performed a prospective observational study in which we categorized telephone calls received by nursing staff over 2 years at a tertiary care IBD clinic (2475 patients in 2009 and 3118 in 2010). We analyzed data on 21,979 ingoing and outgoing calls in 2009 and 32,667 calls in 2010 and assessed associations between clinical factors and logged telephone encounters, and between patterns of telephone encounters and future visits to the ED or hospitalization.

RESULTS: Telephone encounters occurred twice as frequently as office visits; 15% of the patients generated >10 telephone encounters per year and were responsible for half of all telephone encounters. A higher percentage of these high telephone encounter (HTE) patients were female, had Crohn's disease, received steroid treatment, had increased levels of C-reactive protein and

rates of erythrocyte sedimentation, had psychiatric comorbidities, and had chronic abdominal pain than patients with lower telephone encounters. The HTE patients were also more frequently seen in the ED or hospitalized over the same time period and in subsequent years. Forty-two percent of patients with >8 telephone encounters within 30 days were seen in the ED

or hospitalized within the subsequent 12 months.

CONCLUSIONS: Based on an analysis of telephone records at an IBD clinic, 15% of patients account for half of all calls. These HTE patients are a heterogeneous group with refractory disease who are likely to visit the ED or be hospitalized.

Keywords: Crohn's Disease; Ulcerative Colitis; Electronic Medical Record; Telephone Calls; Short Inflammatory Bowel Disease Questionnaire; Anxiety; Depression.

elephone communication is essential in modern society and to healthcare delivery in the United

States. Management of complex chronic diseases requires regular office visits; occasional emergency department (ED) use and/or hospitalizations; and frequent telephone communication among patients, healthcare providers, pharmacies, and insurers. The inflammatory bowel dis- eases (IBD; Crohn's disease [CD], ulcerative colitis [UC]) are lifelong chronic immunologically mediated inflam- matory disorders of the gastrointestinal tract with vari- able clinical courses ranging from mild abdominal

symptoms to life-threatening illness.1,2 Telephone communication in IBD care is common, and involves reporting clinical status, treatment, reassurance, and completion of healthcare forms and insurance authoriza- tion. There is limited information on telephone activity

Abbreviations used in this paper: CD, Crohn's disease; CI, confidence interval; CRP, C-reactive protein; ED, emergency department; EMR, electronic medical record; ESR, erythrocyte sedimentation rate; HTE, high telephone encounter; IBD, inflammatory bowel disease; LTE, low telephone encounter; OR, odds ratio; SIBDQ, short inflammatory bowel disease questionnaire; UC, ulcerative colitis.

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volume or the reasons for calls in the care of chronic illness, including IBD.3–5 Systematic study of telephone encounters as a predictor of adverse outcomes, such as imminent ED use and/or hospitalization, in IBD has not been pursued.

We hypothesized that telephone activity in patients with IBD would be associated with active inflammation and/or difficulty in coping with their illness because of chronic pain and psychiatric comorbidity, and that increased telephone activity might function as a "red flag" identifying patients at risk of high-cost medical interventions, such as ED use and/or hospitalization.

Methods

The study was performed in a tertiary referral IBD clinic where patients contacted the center via telephone regarding questions or concerns involving their care and health status. Nursing personnel handled all routine telephone calls involving the clinic population. There is approximately a 1:1 ratio of nursing support for each physician.

Telephone activity was quantified in two cohorts. In the first, all telephone calls received and performed by nursing staff were prospectively tabulated over a 2-year time period. Telephone calls were categorized into 6 groups: (1) problem/follow-up (patients calling into the center), (2) resolution/plan (nurse calls out of the cen- ter), (3) refill request/pharmacy contact, (4) insurance authorization, (5) completion of forms, and (6) record requests. Calls made or received by nursing staff were tallied; answered and unanswered calls and answering machine messages were included.

The second measure analyzed telephone encounters logged into the electronic medical records (EMR) in consented subjects from a prospective IBD research registry. An initial analysis of the mean number of tele- phone encounters per year was calculated to determine the categories of annual telephone encounters for sub- sequent analysis.3 Patients were stratified based on the rates of annual telephone encounters: 0–1 telephone encounters per year (low telephone encounters [LTE]), 2–5 telephone encounters per year, 6–10 telephone

encounters per year, and >10 telephone encounters per year (high telephone encounters [HTE]). Patient data

abstracted from the EMR included demographics, type of IBD (ie, CD vs. non-CD [UC and indeterminate colitis]), duration of disease (years), history and number of IBD surgeries (lifetime), annual number of clinic encounters, ED visits and hospitalizations, active medications, laboratory parameters, and history of neuropsychiatric comorbidity (ie, anxiety,

depression, chronic pain). Psy- chiatric comorbidity was determined by review of treat- ing physician records as documented in the EMR.

An IBD-specific quality-of-life measure (valid for both CD and UC), the Short Inflammatory Bowel Disease Ques- tionnaire (SIBDQ), was obtained prospectively at each clinic visit. The SIBDQ total score ranges from a low score of 10 (poor quality of life) to a highest score of 70 (excellent

quality of life) in 10 categories reflecting bowel symptoms, systemic and social function, and emotional well-being.6 A patient-specific mean SIBDQ total score generated from all annual clinic encounters was used to dichotomize the study

population into those with a mean score of 2'.50 (good quality of life) from those with a score <50 (poor quality of life).7,8 In addition, we analyzed component data from an

SIBDQ abdominal pain subscore to dichotomize patients into groups with more and less abdominal pain. The abdominal pain score ranges from 1 (all of the time) to 7 (none of the time). A mean annual score was generated and a value of <5 was used to define more frequent abdominal pain, which was labeled chronic abdominal pain.

Active inflammation during the calendar year was approximated by identifying elevation in the serologic biomarkers C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), which reflects inflammatory activity in IBD.9 We analyzed all CRP and ESR values obtained over the course of 1 year and then categorized the patient into 1 of 2 groups: those with all normal values and those with any elevation detected.

Statistical Analysis

Pearson chi-square test was performed to assess as- sociations across the 4 categories of telephone call fre- quencies. One-way analysis of variance was used to test for overall differences between the 4 categories' means. Post hoc comparisons using the Bonferroni test were used to determine if there were significant pair-wise differences between the means of the 4 categories of

telephone call frequencies. All tests were 2-sided, with statistical significance set at a ¼ .05. Univariable logistic regression was performed to assess associations between telephone encounters (HTE vs. non-HTE) and hospital admissions/ED visits among patients from 2009 followed into 2010. The relationship between number of telephone calls in a 30-day period (1, 2–4, 5–7, or 2'.8 telephone calls in a 30-day period) and patient risk of hospital admission or ED visit over the subsequent 12 months was assessed with Kaplan- Meier analysis and Cox regression adjusting for medications (biologics and/or immunomodulators). Data were analyzed using SPSS Statistical Software

(Version 20.0; IBM, Armonk, NY) and Stata Statistical Software (Version 12; StataCorp LP, College Station, TX). This study was approved by the University of Pittsburgh Institutional Review Board (Protocol #012090284).

Results

The IBD center cared for 2475 patients in 2009 and 3118 in 2010, which corresponded with 21,979 ingoing and outgoing calls in 2009 and 32,667 calls in 2010. No specific month demonstrated peak telephone activity during the 2-year study period (Figure 1A).

The telephone activity pattern remained stable over the 2-year period: 52% patient-generated calls regarding

Figure 1. (A) Monthly log of outgoing and incoming telephone activity recorded by nursing staff at an IBD center during 2009 and 2010. The rise in call volume corresponded with a 26% rise in the IBD center's patient population from 2475 patients in 2009 to 3118 patients in 2010. (B) Telephone activity prospectively recorded in categories by nursing staff in 2009 and 2010.

(C) Distribution of IBD registry patients based on their patterns of annual telephone encounters logged in the EMR in 2009 and 2010. Patients with IBD were grouped into 4 categories: 0–1 calls per year (LTE), 2–5 calls per year, 6–10 calls per year, and

>10 calls per year (HTE). (D) Distribution of total telephone encounters across the 4 categories of annual telephone encounter frequency. Patients in the LTE group were responsible for only 2% of the total number of telephone encounters in both 2009

and 2010. In contrast, patients in the HTE groups (15%–16% of the total IBD registry population [C]) were responsible for half of the telephone encounters each year.

a problem or follow-up, 25% nurse-generated calls with a resolution or plan, 12% refill requests, 10% insurance authorizations, and 1% form completion and record re- quests. The mean number of calls handled by nursing staff annually involving all aspects of patient care was

8.9 in 2009 and 10.5 in 2010 per patient (Figure 1B).

Telephone Encounters in Inflammatory Bowel Disease: Patient-specific Characteristics

A consented subgroup of patients (IBD registry; 52% female) was used to analyze specific clinical character- istics associated with EMR recorded telephone encoun- ters. In 2009, 764 IBD registry patients were responsible for 4401 telephone encounters logged in the EMR (mean number of telephone encounters per patient, 5.8 ± 6.5

standard deviation; range, 0–41) and 87.3% of the pa- tients had at least 1 telephone encounter during that year. In 2010, 801 registry patients were responsible for 4500 telephone encounters (mean number of telephone encounters per patient, 5.6 ± 7.1 standard deviation; range, 0–61) and 82.8% of these patients had at least 1

telephone encounter. Telephone encounters occurred twice as frequently as office visits, which totaled 1810 in 2009 and 2007 in 2010.

Stratification of Patients With Inflammatory Bowel Disease by Telephone Encounter Frequency

IBD registry patients were stratified based on fre- quency of telephone encounters. The LTE patients (0–1 total calls per patient per year) represented 26.7% of the

total registry population in 2009 and 30% in 2010. Although these individuals comprised more than one- quarter of the study population, they were responsible for only 2% of telephone encounters each year. The pa- tients with IBD with HTE (>10 total calls per patient per year) were 16% of the registry population in 2009 and

15% in 2010. These HTE patients with IBD were respon- sible for a disproportionate percentage of telephone en- counters, which ranged from 48% in 2009 to 51% in 2010 (Figure 1C and D).

This pattern of HTE activity in the patients with IBD was dynamic over time. Only 32% of the HTE patients with IBD seen in 2009 who were followed into 2010 remained in the HTE category, whereas the remaining 68% of patients dropped into lower telephone encounter categories.

Clinical Factors Associated With Telephone Encounters in Inflammatory Bowel Disease

Increased telephone encounters were associated with female gender, a diagnosis of CD (Table 1), a greater number of previous IBD surgeries, and with an increased number of yearly clinic visits (Table 2). HTE patients had an average of 5 clinic visits compared with an average of 1 for the LTE patients (P < .001) (Table 2). Chronologic

age and duration of IBD were not associated with

increased telephone encounters (Tables 1 and 2). Dis- ease severity was approximated by need for treatment with anti–tumor necrosis factor biologic therapy, which was associated with increased telephone encounters in patients with CD but not UC (Table 1).

Active inflammation was demonstrated in subgroups of patients with IBD, which included CRP elevation (32.2% in 2009 and 32.9% in 2010), ESR elevation

(23.1% in 2009 and 25.8% in 2010), and prednisone

use (28.5% in 2009 and 28.2% in 2010). Increased yearly telephone encounters were associated with increased inflammatory activity, including CRP elevation (P < .001), ESR elevation (P < .001), and prednisone

prescriptions (P < .001) (Figure 2A and Supplementary

Table 1).

There were subgroups of patients with IBD with chronic abdominal pain (38.2% in 2009 and 36.6% in

2010), narcotic use (14.3% in 2009 and 17.1% in 2010), and neuropsychiatric comorbidity (28% in 2009 and 27.1% in 2010). Increased telephone encounters were associated with higher levels of abdominal pain (P <

.001), narcotic prescriptions (P < .001), and neuropsy-

chiatric comorbidity (P < .001) in both years (Figure 2B and Supplementary Table 1).

IBD registry patients with poor quality of life included 40.6% in 2009 and 38.7% in 2010. Quality of life was worse among subjects with greater telephone encounters (P < .001) (Figure 2C and Supplementary Table 1) compared with patient groups with lower number of telephone encounters in 2009 and 2010.

Association of Telephone Encounters With Health Care Use: Emergency Department Visits and/or Hospitalizations

In 2009, 16.3% of IBD registry patients were seen in the ED. The frequency of ED use was 6.4% of the LTE group, 13.6% of the 2–5 calls per year group, 18.2% of the 6–10 calls per year group, and 36.4% of the HTE (c2[3] P < .001). Approximately 16% of the 2009 IBD registry patients required hospitalization. This included

3.9% of the LTE patients, 13.2% of the 2–5 calls per year group, 20% of the 6–10 calls per year group, and 39.7% of the HTE patients (c2[3] P < .001). Similar patterns of ED use and/or hospitalization were identified in 2010 (Figure 2C).

We analyzed the relationship between inflammation, chronic abdominal pain, and psychiatric comorbidity in the IBD registry patients requiring hospitalization in 2009 and 2010. Venn diagrams demonstrating the over- lap of these clinical factors are shown in Supplementary Figure 1. Among the 2009 HTE patients requiring hos- pitalization, an overlap of inflammation, pain, and psy- chiatric comorbidity was identified in 23% (11 out of 48) of these individuals (Supplementary Figure 1A) compared with 6% of the non-HTE patients (5 out of 77;

P < .01; Supplementary Figure 1B). This pattern was also seen in 2010, where inflammation, pain, and psychiatric

comorbidity was found in 31% of the hospitalized HTE patients (14 out of 45) compared with 6% of the hospi- talized non-HTE patients (6 out of 106; P < .001).

Patterns of Telephone Encounters and Subsequent Emergency Department Visits and/or Hospitalization

HTE patients in 2009 had a higher probability of ED use (odds ratio [OR], 2.24 [95% confidence interval (CI), 1.42–3.53]; P < .001) and hospitalization (OR, 1.65 [95%

CI, 1.01–2.68]; P ¼ .04) in 2010 compared with LTE

patients. We examined the relationship between clusters

of telephone encounters and subsequent ED use and/or hospitalization. The maximum number of telephone en- counters over any 30-day time period was identified in the 2009 patients and patterns of ED use and/or hospi- talization over the ensuing 12 months were character- ized (1 telephone encounter per 147 patients [25.6%],

2–4 telephone encounters per 301 patients [52.4%], 5–7

telephone encounters per 95 patients [16.6%], and 2'.8 telephone encounters per 31 patients [5.4%]). Increasing telephone activity over 30 days was associated with subsequent ED use and/or hospitalization (log rank P < .001) (Figure 3). After adjusting for biologic and/or immunomodulator therapy (via a Cox regression model), there was a statistically significant increase in the risk of ED use and/or hospitalization for patients with 5–7

telephone encounters (hazard ratio, 2.53; P ¼ .003; 95% CI, 1.37–4.65) and 2'.8 telephone encounters (hazard

Figure 2. Increasing annual telephone encounters in patients with IBD were associated in both 2009 and 2010 with (A) CRP elevation (P < .001), increased ESR (P < .001), prednisone use (P < .001); (B) abdominal pain (P < .001), narcotic use (P < .001), neuropsychiatric comorbidity (P < .001); and (C) poor quality of life (P < .001), ED visits (P < .001), and hospital admissions (P < .001).

ratio, 3.86; P < .001; 95% CI, 1.84–8.09) compared with those with only 1 telephone encounter (Table 3).

Discussion

Telephone communication is essential in modern so- ciety as an estimated 85% of American adults use cell phones regularly,10 but there is limited information regarding the scope and characteristics of telephone ac- tivity in the care of a specific chronic illness. In this analysis of telephone activity in the care of patients with IBD, we identified the following: (1) the total number of telephone calls in the overall care of a patient with IBD averages 8–10 per year; (2) more than 10% of annual telephone activity involves insurance authorization and healthcare form completion; (3) telephone encounters logged in the EMR are twice as common as office visits;

(4) the distribution of telephone encounters among pa- tients with IBD is skewed with one-sixth of the patient population accounting for half of telephone encounters;

(5) more than 10 telephone encounters annually (HTE) in IBD is associated with female gender, increased inflammatory activity, corticosteroid administration, abdominal pain, narcotic use,11,12 concomitant psychiat- ric illness, and poor quality of life; and (6) HTE corre- sponds with increased healthcare use (clinic visits, ED use and/or hospitalizations) during the same year and may function as a predictor of high use in subsequent years. Thus, telephone activity in IBD, specifically the record of telephone encounters in the EMR, may function as a surrogate marker of disease severity and the ability of patients to cope with their illness as well as a harbinger of impending high-cost healthcare use.

Early investigation of telephone activity in health care sought to determine the patterns of telephone

Figure 3. Relationship between the maximum numbers of patients with IBD telephone encounters over 30 days and subsequent ED use and/or hospitalization over the next 12 months (Kaplan-Meier plot). Increasing telephone activity over 30 days was associated with subsequent ED use and/or

hospitalization (log rank $P < .001$).

consultations provided by physicians, and also evaluated the potential role of telephone encounters as a strategy to decrease the need for office visits as a cost-containing measure.13 More recent studies have investigated smaller populations of patients to determine the clinical characteristics of high-frequency calling patients and patients who call after hours.14 Our study attempted a more ambitious goal, specifically characterizing the entire spectrum of telephone activity occurring in the care of patients with a specific chronic illness over a multiyear time period, focusing on calls handled by nursing support staff.

Our study has several important implications. The ability to optimally monitor clinical status in IBD care, to gauge treatment effectiveness, and to predict which pa- tients are at risk of complications is an important and active area of investigation. Although the inflammatory biomarker CRP is routinely available and often helpful, it was elevated in only 32.2% of IBD outpatients during 2009 and in 58% of those who required hospitalization during that year. Likewise, ED use and/or hospitalization are objective markers identifying more severe IBD, but these events occur too late to function as early markers

of at-risk patients. We found that telephone encounters recorded in the EMR functioned well as an easily iden- tifiable "red flag," pinpointing patients with IBD strug- gling to cope with their illness, because we instruct our patients to call the office if they need assistance. Sec- ondly, our study demonstrates that patients with IBD with HTE suffered from heterogeneous clinical issues, which included increased inflammatory activity, chronic pain, and comorbidities of anxiety or depression.15,16 These findings are in agreement with a randomized controlled trial investigating immunosuppressive treat- ment in CD demonstrating that 18% of enrolled patients who qualified based on self-reported well-being, abdominal pain, and diarrhea failed to demonstrate objective evidence of inflammation on endoscopic assessment.17 HTE was a simple clinical marker of pa- tients with IBD at risk of deterioration requiring high- cost ED assessment and/or hospitalization during the same and subsequent calendar years. Thus, monitoring of telephone activity in the care of IBD may function as a clinical "barometer," identifying patients at risk of deterioration and needing high-cost care. What is un- known is whether these heterogeneous, at-risk, HTE patients with IBD could be targeted for tailored in- terventions that would more effectively address the specific clinical factors (ie, refractory inflammation, pain, psychiatric comorbidity) that were contributing to their poor clinical status.

There were several strengths to our study. We accu- mulated 2 years of comprehensive data regarding all patients followed in a large chronic disease management clinic and supplemented this with additional information from a consented registry with prospectively accumu- lated data. The similar patterns of annual telephone ac- tivity over both years served as an internal validation of our research strategy. However, there were important limitations in our study.

Our findings were generated from a single referral center and a subgroup of research registry patients and may not be reflective of the general IBD population. Our stratification of call volume was arbitrarily based on the average number of annual calls per patient. In addition, we stratified patients with IBD

Table 3. Hazard Ratios for ED Use and/or Hospitalization in Patients With IBD Stratified by 30-Day Telephone Encounter Patterns

	Total n	Hazard ratio	P value	95% CI
2–4 telephone encounters	301	1.61	.08 (NS)	0.94–2.78
5–7 telephone encounters	95	2.62	.002	1.43–4.82
2'.8 telephone encounters	31	1.58	.000	2.08–8.85
Adjusting for medications (biologics and/or immunomodulators)				
2–4 telephone encounters	301	1.60	.08 (NS)	0.92–2.77
5–7 telephone encounters	95	2.53	.003	1.37–4.65
2'.8 telephone encounters	31	3.86	.000	1.84–8.09

NOTE. Cox regression was used to determine the association of telephone calls over 30 days and risk of ED use and/or hospitalization over the next 365 days. After adjusting for medications, the association of telephone call clusters and increased risk for ED use and/or hospitalization was significant for both the 5–7 telephone encounter cluster (hazard ratio, 2.53 [95% CI, 1.37–4.65; P ¼ .003]) and for patients with 8 or more telephone encounters over a 30-day period (hazard

ratio, 3.86 [95% CI, 1.8–8.09; P < .001]). The patient group with 1 telephone call over 30 days (n ¼ 147) comprised the reference population.

based on patterns of laboratory findings (ie, CRP eleva- tion), mean quality-of-life scores, mean pain scores, and patterns of corticosteroid and narcotic use, which are reasonable clinical markers, but have not been well validated as measures of severity in IBD clinical inves- tigation. We chose this approach because there is no uniformly accepted IBD severity index that accurately reflects the long-term burden of illness experienced by patients.18 Correlating poor clinical

outcome with tele- phone calls in patients who are instructed to contact our clinic if they are experiencing problems can be criticized as being tautologic. We acknowledge this, but point out that the goal of our study was to identify a common clinical "red flag" that would function for all heteroge- neous subgroups of patients with IBD (ie, those suffering from inflammation, pain, and/or psychiatric comorbid- ity) who were at risk of complications. Our findings were strengthened by the demonstration of a substantial lag between the increased cluster of telephone encounters in patients with IBD and subsequent ED use and/or hos- pitalization, suggesting an opportunity for intervention and/or prevention.

The rationale for characterizing telephone activity in patients with IBD was two-fold. In addition to identifying a clinical "barometer" that would function to gauge clinical status, we also sought to quantify the currently unrecognized and unreimbursed effort that is made by clinic support staff in handling telephone calls in the care of IBD. Our report underscores the importance of tele- phone communication based on the sheer volume of calls, their ability to predict costly hospital-based care, and highlights a need to recognize and support this infrastructure. Greater than 10% of telephone commu- nication handled by nursing staff involved insurance authorization and healthcare form completion. The sub- stantial telephone effort required for insurance authori- zation may represent an important area for improving efficiency of healthcare delivery.

Overall, our report highlights the analysis of tele- phone activity as a novel strategy to gauge clinical status and provide insight into the contributing factors that drive increased healthcare use in IBD. More importantly, increased telephone encounters recorded in the EMR may function as an early warning mechanism to identify at-risk patients with IBD who may benefit from improved inflammatory and multidisciplinary treatment.

Supplementary Material

Note: To access the supplementary material accom- panying this article, visit the online version of Clinical Gastroenterology and Hepatology at www.cghjournal.org, and at http://dx.doi.org/10.1016/j.cgh.2013.11.015.

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G. Binion had full access to all of the data in the study and takes re- sponsibility for the integrity of the data and the accuracy of the data analysis.

Conflicts of interest

The authors disclose no conflicts.

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Supplementary Figure 1. The relationship of inflammation, chronic pain, and psychiatric comorbidity in hospitalized patients with IBD stratified by telephone activity in 2009. HTE patients with IBD who required hospitalization are shown in panel A (n ¼ 48), and all remaining hospitalized patients in lower telephone frequency categories (non-HTE) are

shown in panel B (n ¼ 77). Venn diagrams demonstrate overlap of inflammation, chronic pain, and neuropsychiatric comorbidity in the HTE patients in 2009 (22.9%) compared with the non- HTE hospitalized patients (6.5%; P < .01).

Liver Transplantation Arrests and Reverses Muscle Wasting

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Abbreviations: BMI, body mass index; CT, computed tomography; MELD, model for endstage liver disease; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; PSC, primary sclerosing cholangitis; SAT, subcutaneous adipose tissue; SMI, skeletal muscle index; TIPS, transjugular intrahepatic portosystemic shunt; VAT, visceral adipose tissue

Abstract

Muscle wasting, sarcopenia, is highly prevalent in advanced cirrhosis and predicts adverse outcomes while awaiting and following liver transplantation. Post-transplant worsening of sarcopenia has attracted recent interest but it is unknown whether this serious problem results from transplantation itself or from confounding conditions such as recurrent allograft liver disease or other muscle wasting post-transplant complications. To clarify this question we studied pre- and post-transplant muscle mass in a retrospective cohort of 40 patients transplanted for 3 diseases—alcoholic cirrhosis,

nonalcoholic steatohepatitis (NASH) cirrhosis, and primary sclerosing cholangitis (PSC) cirrhosis—in whom allograft disease recurrence was monitored and excluded, and who lacked common post-transplant muscle wasting complications such as sepsis, renal failure, ischemia and cholestasis. We measured skeletal muscle index (SMI) using computed tomography (CT) before and 12-48 months after transplant. SMI as a categorical variable significantly improved, from 18 patients above the normal cutoff pre-transplant to 28 post-transplant ($p=0.008$). SMI increases were greatest in patients with the lowest pre-transplant SMI ($p<0.01$). As a continuous variable, mean SMI remained stable, with a nonsignificant trend toward improvement. Our data show that muscle wasting does not progress but is arrested and frequently improves after liver transplantation in the absence of confounding events.

Introduction

Muscle wasting is a common and serious manifestation of advanced cirrhosis. Deficient skeletal muscle mass measured on body imaging, termed sarcopenia, predicted death after liver transplantation in 3 recent reports (1-3), and nonlethal post-transplant morbidity in another study (4). Sarcopenia also predicted death in patients evaluated for or awaiting transplantation (5-7). Muscle mass had predictive value independent of other indicators of liver disease severity such as Model for Endstage Liver Disease (MELD) score and Child class.

Whether sarcopenia worsens, persists, or recovers after liver transplantation has accordingly attracted growing interest, as shown in an analysis of post-transplant sarcopenia reported in 6 studies involving 304 patients (8). Potential causes of post-transplant sarcopenia cited in that review included ongoing signaling by a muscle wasting mediator, myostatin; persistent disturbances involving the metabolic syndrome; adverse effects of immunosuppression and muscle wasting complications such as sepsis, cholestasis and renal failure; and allograft recurrence of such diseases as hepatitis B and C, autoimmune hepatitis, and nonalcoholic fatty liver disease. A new study of pre- and post-transplant muscle mass using computed tomographic (CT) imaging reported that sarcopenia regularly worsened after transplantation in 53 patients (9).

Given the clinical importance of understanding mechanisms involved in post-transplant sarcopenia, a central question is whether the problem is an obligate consequence of transplantation itself or results from the confounding conditions listed above. In order to answer this question accurately, we evaluated skeletal muscle mass before and after liver transplantation in 40 patients selected for absence of potentially confounding influences on skeletal muscle mass in the post-transplant period.

Methods

Patients

This retrospective observational cohort study was approved by the University of Pittsburgh Institutional Review Board under protocol O12030073. We selected a cohort of all patients who had analyzable serial abdominal CT imaging obtained before and between 12 and 48 months after an initial liver transplant performed for alcoholic cirrhosis, nonalcoholic steatohepatitis (NASH) cirrhosis, or primary sclerosing cholangitis (PSC) with cirrhosis. We chose these 3 diseases because their post-transplant recurrence in the observation period between transplantation and a follow-up scan could be excluded by clinical monitoring for relapse in the case of alcoholic cirrhosis, or by review of post-transplant imaging in the case of NASH and PSC.

As shown in Figure 1, 547 patients had an initial liver transplant for alcoholic cirrhosis, NASH cirrhosis, and PSC cirrhosis among the 2061 transplants performed at our center from 2000 to 2012. We did not study patients with combined liver/kidney, multivisceral, or repeat transplants. Patients were not included if they had evidence of coexisting hepatitis B or C infection or other alternative causes of cirrhosis in their pre-transplant evaluation. We did include patients in whom a hepatocellular carcinoma confined to the native explanted liver was present if there was no evidence of recurrence or metastasis in the post-transplant observation period.

Of these 547 patients, 152 had a clinical record of abdominal CT imaging before and between 12 and 48 months after transplant. Post-transplant scans were performed for clinical indications such as abdominal distress, evaluation of potential abdominal inflammation or infection, or concern for recurrent hepatocellular carcinoma or other tumors. Pre- and post-transplant images were available in our picture archiving and communication system for 48 of these patients for body composition analysis.

We reviewed the records of these 48 patients using predefined criteria to exclude those with potentially confounding causes of post-transplant muscle wasting. Exclusion criteria were any critical care unit readmission in the post-transplant observation period, hepatic artery thrombosis/ischemic cholangiopathy, alcohol relapse, persistent renal failure with creatinine above 2 mg/dL, post-transplant lymphoproliferative disorder, opportunistic infection requiring hospitalization, post-transplant imaging suggesting either allograft PSC recurrence by presence of typical duct abnormalities or nonalcoholic fatty liver disease (NAFLD) by presence of steatosis, and new malignancy or recurrent hepatocellular carcinoma. We excluded 8 patients, including 2 with PSC recurrence, 2 with de novo cancers (1 lung, 1 colon), 2 with renal failure, 1 with alcohol relapse and 1 with severe recurrent acute pancreatitis and mesenteric vein thrombosis. The 40 remaining patients comprised our study cohort.

Body Composition Analysis

We measured skeletal muscle as the skeletal muscle index (SMI), and measured visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT), using segmentation analysis of cross sectional CT images at the midpoint of the third lumbar vertebra. Measurements were expressed as surface area in cm^2 divided by the square of patient height in m^2 as previously reported (1-6). In order to define presence or absence of sarcopenia as a categorical variable, we used previously reported SMI cutoff levels for sarcopenia of $<38.5\ cm^2/m^2$ in women and $<52.4\ cm^2/m^2$ in men (5).

We used the MITK software package, an open source application for body segmentation developed by the German Cancer Research Institute (10). MITK is similar to applications such as the commercial Slice-O-Matic and the open source NIH ImageJ software packages; the latter have been compared and found to produce congruent results (11). We found that intra-observer reproducibility for the MITK package was satisfactory, with serial measurements within 5 percent of each other (data not shown). We assessed inter-reader agreement for MITK among 3 observers for measurements of SMI, VAT, and SAT as described by Bland and Altman (12). Contrast-enhanced CT scans from 40 healthy living organ donor candidates (20 men and 20 women) were analyzed by each observer. As shown in Supplementary Table 1, intra-class correlations, mean measurement differences, and coefficients of repeatability were acceptable and comparable with previously published analyses of body composition software performance (11, 13).

Statistical Analysis

For each of the variables of interest—SMI, VAT, and SAT--data were described before and after transplant. For SMI, the cutoffs noted above were used to categorize sarcopenia as present or not. Normal quantile plots were visually inspected to assess whether data were at least approximately normal. Paired differences were tested using a paired t-test and paired differences between categories for sarcopenia were tested using McNemar's test (14). McNemar's test measures whether the discordance (at say time 1 versus time 2) is beyond what would be expected by chance. Paired t-tests were done overall and repeated within gender and within condition (i.e. alcoholic cirrhosis, NASH and PSC). McNemar's test was not repeated within groups, given the small counts in the resulting contingency tables.

Linear regression analysis was conducted to assess the significance of potential associations of disease diagnosis, age, sex, MELD score, BMI, and waiting list time to transplant (adjusting for the other variables in the model) for predicting the paired differences in the continuous measures from before to after transplant (i.e. post-transplant value minus pre-transplant value). The coefficients for the linear regression thus represent the association between values (or categories) of a given variable and the paired differences, where a positive coefficient represents a larger change in post- minus pre-transplant difference. For comparison of disease groups, NASH was used as the baseline category so that the coefficients for the alcoholic and PSC groups were compared with the NASH group using the F statistic. Variables which were at least marginally significant (i.e. $p \leq 0.10$) in the unadjusted analysis, or in the analysis adjusted for initial muscle mass, were included in a multivariable model. Variables that achieved a p-value of $p \leq 0.05$ in the multivariable model were considered statistically significant. Use of logistic regression as an alternative to linear regression in the case of binary outcomes was considered for modeling the binary categorical measure of sarcopenia, but the sample size was insufficient for doing so (given that at least 10 events of sarcopenia are needed for each variable and presence of sarcopenia would also have to be adjusted for in the model). All analyses were run in STATA statistical software.

Results

Baseline data for the 40 patients comprising our study cohort are shown in Table 1. There were 9 patients, all men, with alcoholic cirrhosis, 21 (10 men and 11 women) with NASH cirrhosis, and 10 (7 men and 3 women) with PSC cirrhosis. There were 5 living donor transplants. Hepatocellular carcinoma confined to the explanted liver was present in 14 patients. The tumor was a new finding on pathologic examination of the explant in 4 patients and detected on pre-transplant imaging in the other 10. Patients with evidence of tumor recurrence or spread during the post-transplant observation period were not included in the study cohort.

Pre- and post-transplant muscle mass expressed as SMI is shown in Table 2. Overall, pre-transplant sarcopenia was prevalent in all groups, especially with PSC cirrhosis, where only 1 of the 10 patients was not sarcopenic prior to transplant. When SMI was considered as a categorical variable, either normal or sarcopenic based on gender-specific cutoffs, 89% of the 18 patients with a normal pre-transplant SMI remained normal post-transplant, and 55% of the 22 patients with a sarcopenic pre-transplant SMI improved to normal. The categorical change was significant ($p=0.008$). As a continuous variable, after transplant the mean SMI in each patient group and overall showed a nonsignificant trend toward improvement compared with pre-transplant values. SMI as a continuous variable did not worsen in any gender or disease subgroup.

An unadjusted linear regression model, a model adjusted for pre-transplant values, and a multivariable regression model are shown in Table 3 for SMI. For change in muscle mass after transplantation, results of the unadjusted linear regression model showed that pre-transplant muscle mass was significantly and negatively associated with the extent of post-transplant change in muscle mass ($p<0.01$). Lower pre-transplant muscle mass was associated with a greater magnitude of post-transplant recovery. After adjusting for pre-transplant muscle mass, both BMI and disease diagnosis were marginally significant and were included in the multivariable model. Only pre-transplant muscle mass was associated with the extent of its change in the multivariable model; as with the unadjusted model, lower pre-transplant muscle mass was associated with a greater post-transplant increase (coefficient -0.92, $p<0.01$).

The time from transplant to the post-transplant CT scan was also checked as a covariate in both the unadjusted models and the models adjusted for the baseline measure. None of the results showed a p-value below 0.22.

Pre- and post-transplant VAT and SAT are shown in Supplementary Table 2. Visceral adiposity increased significantly after transplantation in patients with NASH cirrhosis and for the entire cohort. Subcutaneous adiposity showed a nonsignificant increase in all disease groups.

Discussion

We found that post-transplant sarcopenia is not an obligate consequence of liver transplantation. SMI improved or stabilized after liver transplantation in our patients in whom confounding causes of muscle wasting and recurrent allograft liver disease were excluded. Improvement was greatest in patients with the most severe pre-transplant sarcopenia.

Our findings contrast with and differ from those of Tsien et al., who reported ongoing post-transplant muscle loss in 53 patients evaluated for sarcopenia with equivalent methods to those we employed and managed with similar post-transplant immunosuppression regimens (9). Sarcopenia increased from 62% of their patients pre-transplant to 87% post-transplant. In our cohort sarcopenia decreased from 55% of patients pre-transplant to 30% post-transplant. A key difference in design of the 2 studies was that patients with known post-transplant muscle wasting conditions and recurrent allograft diseases were not reported as excluded from Tsien et al.'s cohort as they were from ours. Taken together with earlier summarized data (8), it appears likely that complicating events and allograft disease recurrence, rather than transplantation itself, will emerge as the major drivers of post-transplant sarcopenia.

Our study's key limitation is related to its intentional exclusion of potentially confounding causes of post-transplant sarcopenia in order to isolate the effect on muscle mass of transplantation alone, so that our patient cohort does not represent the general transplant population in whom these problems are frequent (8). In addition, the need for a clinically indicated post-transplant CT scan influenced patient selection. It appears unlikely, however, that need for post-transplant imaging based on concerns for pain, infection, inflammation or recurrent cancer would have generated bias toward the improvement and stabilization in muscle mass that we observed.

Our findings of ongoing visceral and subcutaneous adiposity are expected in light of current knowledge of the post-transplant state (15).

Muscle mass as an indicator of advanced liver disease severity and prognosis is attracting increasing recognition (16, 17). A new molecular connection between cirrhosis and sarcopenia is stimulation by elevated ammonia levels of muscle cell production of myostatin, a potent mediator of muscle wasting (18). After successful placement of a transjugular intrahepatic portosystemic shunt (TIPS), improved functional status is associated with improved muscle mass (19). Therapeutic interventions that promote recovery of muscle mass in other sarcopenic diseases have been shown to improve performance and quality of life (20).

Although the clinical and prognostic value of muscle mass is well described, it is not clear whether anatomic muscle mass measurements should become a therapeutic target for improving physical conditioning in cirrhosis. A review of 13 studies of exercise to improve physical performance in cirrhosis, for example, highlighted performance measurements of aerobic capacity and gait speed as important clinical endpoints (21). A new report described similar high prognostic value of physical performance testing in liver transplant waitlisted patients (22). In appropriate settings both anatomic muscle mass and physical performance measurements may have complementary value.

To conclude, our findings challenge the concept that sarcopenia should be expected as an obligate consequence of liver transplantation. We found that successful liver transplantation without confounding muscle wasting complications improves and stabilizes muscle mass, a critical observation for guiding efforts to prevent and reverse transplant-related muscle wasting. Reversal of sarcopenia after transplantation should be considered an achievable goal.

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Disclosures

The authors have no conflicts of interest to disclose.

Figure Legend

Figure 1. Selection of a Patient Cohort For Pre- and Post-Liver Transplant Measurement of Muscle Mass

Description of Supporting Information

Supplementary Table 1. Inter-reader agreement among 3 observers for measurements of skeletal muscle index (SMI), subcutaneous adipose tissue (SAT), and visceral adipose tissue (VAT).

Supplementary Table 2. Visceral and subcutaneous adipose tissue before and after liver transplantation.

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Tables

Table 1. Baseline Data for 40 Patients With Liver Transplants for Alcoholic, NASH, and PSC Cirrhosis

Disease	Age	BMI	MELD	Albumin	HCC	Living Donor	Waitlist Time, Months	Time from Transplant to Second CT, Months
Alcoholic Cirrhosis 9 men	59.6 ± 7.0	27.6 ± 5.0	18.8 ± 7.0	3.0 ± 0.3	5	0	4.1 ± 5.1	20.3 ± 7.4
NASH Cirrhosis 10 men, 11 women	58.0 ± 10.6	32.3 ± 5.9	12.8 ± 3.7	3.0 ± 0.5	8	4	3.7 ± 2.6	23.9 ± 9.5
PSC Cirrhosis 7 men, 3 women	52.0 ± 12.9	25.1± 2.9	16.4 ± 7.6	3.1 ± 0.7	1	1	2.4 ± 0.9	24.7 ± 10.7
Total 26 men, 14 women	56.8 ± 10.9	29.4 ± 6.0	15.1 ± 6.2	3.0 ± 0.5	14	5	3.5 ± 3.2	23.3 ± 9.6

Data are means ± 1 SD

Table 2. Skeletal Muscle Index (SMI) Before and After Liver Transplantation

Liver Disease	Skeletal Muscle Index, cm^2/m^2		P value
	Pre-transplant	Post-transplant	t-test
Alcoholic cirrhosis n=9, men	51.2 ± 9.6 4/9	56.8 ± 6.4 6/9	0.16
NASH cirrhosis n=10, men	43.9 ± 9.9 6/10	49.1 ± 5.6 8/10	0.66
PSC cirrhosis n=7, men	45.0 ± 4.4 0/7	46.6 ± 8.4 2/7	0.72
All men n=26	52.1 ± 12.0 10/26	55.7 ± 12.3 16/26	0.26
NASH cirrhosis n=11, women	43.9 ± 9.9 7/11	49.1 ± 5.6 11/11	0.11
PSC cirrhosis n=3, women	34.6 ± 5.5 1/3	37.8 ± 12.2 1/3	0.58
All women n=14	41.9 ± 9.9 8/14	46.7 ± 8.8 12/14	0.07

Values in each cell are mean ± SD followed by the number of patients/total with normal skeletal muscle index above the cutoff levels of 52.4 cm^2/m^2 in men and 38.5 cm^2/m^2 in women.

The overall categorical change after transplant from 18 to 28 in the number of patients with SMI above the normal cutoff was significant at p=0.008 by McNemar's test.

When assessed as a continuous variable, there were no significant differences between mean pre- and post-transplant SMI values in any patient group, based on continuous paired differences and the paired t-test. Post-transplant SMI did not worsen in any gender or disease group.

Table 3. Linear Regression Model for Change in Muscle Mass

	Unadjusted Linear Regression		Linear Regression Adjusted for Pre-Transplant Muscle Mass		Multivariable Linear Regression	
Variable	Coefficient (p-value)	95% CI	Coefficient (p-value)	95% CI	Coefficient (p-value)	95% CI
Age	.073 (0.72)	-.34, .48	-.033 (0.85)	-.38, .31	---	---
Sex	1.19 (0.80)	-8.23, 10.60	-6.36 (0.13)	-14.59, 1.87	---	---
MELD	.24 (0.51)	-.48,.95	.13 (0.66)	-.47, .73	---	---
BMI	-.32 (0.39)	-1.06, .42	.70 (0.06)	-.030, 1.44	.70 (0.09)	-.13, 1.53
Waitlist Time	.53 (0.45)	-.88, 1.94	.86 (0.14)	-.29, 2.01	---	---
Muscle Mass*	-.64 (<0.01)	-.94, -.34	---	---	-.92 (<0.01)	-1.28, -.56
Disease Type**	(0.86)		(0.10)		(0.15)	
Alcoholic	1.24 (0.83)	-10.20, 12.68	1.73 (0.70)	-7.21, 10.67	5.19 (0.28)	-4.43, 14.81
PSC	-2.24 (0.68)	-13.27, 8.79	-8.67 (0.06)	-17.68, .34	-5.14 (0.29)	-14.86, 4.58

*Pre-transplant muscle mass

**With NASH as the baseline; the p-value in the Disease Type row is for the overall F-test

--- Denotes variables not included in the given model

Title: Impact of obesity on inflammatory bowel disease:

Metabolic, clinical and therapeutic implications

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Abbreviations: IBD, inflammatory bowel disease; SIBDQ, short inflammatory bowel disease questionnaire

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Study Highlights

1. What is current knowledge:
   - Obesity has risen to epidemic proportions affecting up to one third of the U.S. adult population.
   - Obesity is associated with significant morbidity and mortality.

- The impact of obesity on IBD has not been characterized.

2. What is new here:
   - Two thirds of our IBD population is over their ideal body weight and one third was obese.
   - Obesity in IBD is associated with ulcerative colitis, poor quality of life, elevated CRP, co-morbidities (hypertension, hyperlipidemia, diabetes mellitus and psychiatric co-morbidity) and polypharmacy.
   - Weight based dosing of purine analog and infliximab was not achieved in the majority of obese IBD patients.

Abstract

Introduction:

Obesity has reached epidemic proportions and its impact on chronic illness, including inflammatory bowel disease (IBD) is not defined. We sought to characterize: i) rates of obesity in IBD, ii) patterns of obesity associated co-morbidities, iii) association of obesity with IBD severity and treatment, and iv) effect of obesity on IBD drug dosing.

Methods:

This was a prospective 3 year study from a referral center and IBD patients were categorized by body mass index (BMI); underweight (BMI <18.5), normal (BMI ≥18.5- <25), overweight (BMI ≥25- <30), and obese (BMI ≥30) including obesity types I (BMI ≥30 - <35), II (BMI ≥35 <40), and III (BMI ≥ 40). IBD related quality of life, co-morbidities, healthcare utilization and treatment were characterized.

Results:

Among 1494 IBD patients, 71.9% were above their ideal BMI and 31.5% were obese. Obesity was more common in ulcerative colitis and obese class II and III patients were predominantly female. Obesity in IBD was associated with diabetes mellitus, hypertension, hyperlipidemia, psychiatric co-morbidity, poor quality of life and increased rates of biochemical inflammation. There was no association between increasing BMI and annual prednisone use, emergency department use, hospitalization and surgery. Increasing BMI was associated with lower mg/kg doses of purine analogs and infliximab.

Conclusions:

The majority of IBD patients are above their ideal BMI and obesity occurred in >30%. Obesity in IBD is associated with worse quality of life, biochemical inflammation, co-morbidities and polypharmacy. Optimal regimens for drug dosing in obese IBD patients have yet to be defined.

Introduction

Excess body weight and obesity have emerged as a major health risk affecting the American population. The World Health Organization (WHO) now lists obesity as one of the top ten risks to overall health. [1] At this time an estimated 68.8% of the American population is either overweight or obese according to the Centers for Disease Control. [2, 3] Obesity has been linked to the rise and severity of illnesses including diabetes mellitus, hyperlipidemia, cardiovascular disease, cancers, and Alzheimer's disease. [1] There is limited information regarding the impact of obesity on chronically ill patients who have historically been at risk of becoming underweight, such as patients suffering from inflammatory bowel disease (IBD).

Crohn's disease (CD) and ulcerative colitis (UC), the major forms of IBD, are lifelong, immunologically mediated disorders categorized by chronic inflammation and progressive damage to the gastrointestinal tract. Patients with IBD typically suffer a waxing and waning clinical course which frequently requires immunosuppressive induction and maintenance therapy with the goal of achieving clinical remission. [4, 5] Up to 75% of CD patients require surgery during their lifetime due to irreversible damage to the intestine that often leads to intermittent partial obstruction. [6] In comparison, a subgroup of severely ill UC patients require colectomy due refractory disease despite medical therapy or the emergence of colonic dysplasia and/or cancer.[6] These multiple clinical factors have typically resulted in IBD patients being at risk for weight loss and subsequently becoming chronically underweight. [7, 8] Indeed, being underweight is a component sub-score in the Crohn's disease activity index (CDAI), which has historically functioned as the optimal metric for assessing the efficacy of CD treatment in clinical investigation. [9] Despite these challenges, there has been substantial clinical progress over the past decade where the use of maintenance immunosuppressive and

biologic regimens have helped the majority of patients with moderate to severe IBD achieve and maintain remission. [10-12]

Obesity has been identified as a potential complicating factor in both medical and surgical management of IBD [6, 7]. The purine analog immunosuppressants azathioprine and 6-mercaptopurine (6-MP) have been administered with weight based dosing, as has the infusion anti-tumor necrosis factor (TNF) agent infliximab. [10, 12-14] However, it is important to be aware that the initial studies evaluating these treatments were performed in past decades prior to the current obesity epidemic. There is limited data at the present time characterizing the impact of obesity on the clinical course of IBD and the inter-relationship between obesity and maintenance drug dosing in IBD.

We hypothesized that rates of obesity and co-morbidities associated with obesity have increased in the U.S. adult IBD patient population, which will negatively impact their clinical course. To test this hypothesis we sought to characterize: 1) the rates of obesity in IBD patients followed in a tertiary-care referral clinic; 2) rates of obesity associated co-morbidities in IBD; 3) impact of obesity on IBD clinical course and 4) IBD drug dosing in the setting of obesity.

Materials and Methods

Patient population

We utilized a consented IBD research registry maintained at the University of Pittsburgh Medical Center (UPMC) which gathers prospective, longitudinal natural history data. IBD Registry patients followed between 2009 - 2011 comprised the study population. In addition to disease and demographic information, the IBD registry gathers prospective data from the electronic medical record (EMR) which includes healthcare utilization (i.e. emergency room (ER) encounters, hospitalizations, etc.), co-morbidities, treatment, laboratories and data regarding clinical status obtained at the time of clinic visits including quality of life scores and disease activity index scores.

Weight characterization: Body mass index (BMI)

The mean weight in kilograms (kg) between 2009 and 2011 was used with the height in meters to calculate the body mass index (BMI) for all IBD patients. BMI is calculated from the individuals weight in kg divided by their height in meters^2 and this has functioned as a reliable indicator of body adiposity and as a screening tool to determine health risk. [15] Normal body weight was defined as a BMI ranging from $\geq$18.5 - <25, with underweight patients having a BMI <18.5. Overweight patients had a BMI ≥25 and <30. Obesity was defined as a BMI ≥30, and this was further sub-classified into three categories: Obese type I: BMI $\geq$30 - <35, obese type II: $\geq$BMI 35 - <40, and obese type III: BMI ≥ 40. [15]

Presence of obesity associated co-morbidities

Obesity is associated with diabetes mellitus, hypertension and hyperlipidemia. The concordance of these illnesses characterizes the metabolic syndrome. [16, 17] We identified the presence of these co-morbidities in our study population by identifying anti-hypertensive prescriptions, diabetic medications (including oral and

injectable hypoglycemic agents defined by the American Diabetes Association) and cholesterol lowering medications endorsed by the American Heart Association (not including bile acid sequestrants, which are commonly used for diarrhea management in IBD).

IBD clinical status: Health related quality of life, prednisone and narcotic utilization, CRP elevation

IBD Registry patients prospectively provide validated metrics at the time of clinic visits, including health related quality of life scores which are recorded in the EMR. Disease related quality of life was measured using a previously published version of the Short Inflammatory Bowel Disease Questionnaire (SIBDQ) and these scores were used to calculate a mean score over the course of an individual calendar year as well as a total mean score over the course of 3 years [18, 19]. Annual and three year rates of hospitalization, ER visits and surgery were recorded as an additional marker of overall health status and disease activity [20].

Prednisone utilization over the course of a calendar year was used as a proxy of inflammatory activity and this information was recorded for each patient. Likewise, narcotic use on an annual basis was tabulated, as this may also function as a marker of poor overall health status [20]. Finally, a summary of all medication use was used to approximate rates of polypharmacy in the IBD patients.

C-reactive protein (CRP) is a biomarker which correlates with increased inflammatory activity in patients with IBD. Patterns of CRP elevation over the course of a calendar year were analyzed, and grouped as one of two dichotomous variables – any CRP elevation detected *vs*. all CRP tests falling within normal range [20]. CRP elevation was defined as a level exceeding 0.7 mg/dL which is the upper limit of normal for our reference laboratory.

IBD maintenance treatment

IBD maintenance medications were identified using prescription data from the EMR. The most recent specific dose and mean patient weight were determined using data between the years 2009 and 2011. Maintenance IBD immunosuppressants that were evaluated included methotrexate, azathioprine and 6-MP. Azathioprine and 6-MP were given as daily oral tablets, while methotrexate was administered weekly either as an oral formulation or as a subcutaneous injection. The anti-TNF drugs that were evaluated included infliximab, adalimumab, and certolizumab pegol. Certolizumab pegol has a standard dosing regimen every four weeks. Infliximab and adalimumab administration frequency are often intensified and the specific patterns of administration were recorded in weeks.

An additional analysis regarding drug dosing was performed using ideal body weight (IBW). IBW was first introduced by Devine in 1974 in order to improve estimation of drug clearance in obese patients. [21] The IBW calculation used to determine IBW was based on the Devine formula and is determined in kg. For men IBW = 50 kg + 2.3 kg for each inch the patient's height is over 5 feet whereas for females IBW = 45.5 kg + 2.3 kg for each inch the patient's height is over 5 feet. [21]

Statistical analysis

Descriptive statistics were used to generate mean and standard deviation within each BMI category for baseline characteristics. Univariate comparisons for binary explanatory variables between baseline characteristic parameters were performed using a Chi-square analysis on gender, disease type, immunomodulator use between 2009-2011, biologic use between 2009-2011, combination therapy from

2009-2011, psychiatric co-morbidity, as well as IBD activity measures including CRP abnormalities (2011), narcotic use (2011), prednisone use (2011), hospitalizations (2011) and ER visits (2011). Continuous explanatory variables for IBD activity such as SIBDQ (2009-2011) and SIBDQ for 2011 were analyzed using ANOVA with Bonferoni adaptation for multiple comparisons. ANOVA with Bonferoni adaptation was also performed to determine significance within the 6 medications analyzed for weight based dosing regimens and white blood cell counts (2009-2011). Chi-square analysis with univariate comparisons were used to compare rates of medical comorbidities (i.e. diabetes, dyslipidemia and hypertension).

Analysis was performed using SPSS version 10 and all data was accumulated through a University of Pittsburgh IRB approved database that has been housed in a HIPAA compliant and secure share drive maintained by the Division of Gastroenterology, Hepatology & Nutrition. This study was approved by the University of Pittsburgh IRB (PRO12110117).

Results

IBD patient characteristics and BMI distribution

A total of 1494 IBD patients formed the study population, and these subjects were stratified by their mean BMI **(Figure 1a, Table 1)**. Overall, 71.9% of the IBD patients were above their ideal BMI and 31.5% were obese. Underweight IBD patients (BMI < 18.5) were rare (1.8% of the cohort) and there were significantly more super-obese (BMI ≥ 40) patients identified (4.4%; $p<0.0001$). Obesity occurred more commonly in UC patients compared with CD patients ($p<0.02$); **(Figures 1b and 1c)**.

There was a significant difference across BMI categories with regards to gender **(Table 1).** Females predominated in underweight, normal weight and obese II and III subgroups while males comprised the majority of overweight and obese category I IBD patients. The mean age varied across the BMI categories with the youngest patients in the underweight and normal weight groups and older patients predominating in the groups above their IBW.

Presence of co-morbidities in IBD patients

Hypertension, diabetes mellitus and hypercholesterolemia were characterized in the IBD patient population stratified by BMI. Rates of these obesity associated co-morbidities rose with increasing BMI ($p=0.001$ for all 3 co-morbidities). Furthermore, IBD patients with class III obesity had the highest rates of these co-morbidities **(Table 1).**

We next analyzed the overlap of these metabolic syndrome defining illnesses across the IBD patients stratified by BMI. The presence of overlapping patterns of hypertension, diabetes mellitus and hypercholesterolemia was significantly associated with rising BMI in IBD **(Figure 2).** Among the class III obese IBD patients 12.3% had all three co-morbidities.

We analyzed patterns of hypercoagulability amongst the IBD patients stratified by BMI using Coumadin treatment as a proxy for clotting. There was no difference in rates of Coumadin exposure during the 2009 – 2011 time periods across the BMI subgroups **(Table 1).**

Psychiatric co-morbidities in IBD patients were identified most commonly in the obese II and III subgroups. In contrast, the lowest rate of psychiatric co-morbidity was seen in the overweight IBD patients **(Table 1).**

Association of BMI with IBD activity, treatment requirement and healthcare utilization

Poor disease related quality of life was seen in increased rates in IBD patients on the extremes of the BMI spectrum. Underweight and obese IBD patients had the highest rates of poor quality of life compared with the normal and overweight patients **(Table 2).**

Rates of CRP elevation differed significantly between the IBD subgroups which were stratified by BMI. The highest rates of CRP elevation were seen in the class III obese IBD patients, where 53.3% were found to have elevated CRP during 2011.

Rates of steroid exposure, approximated by the percentage of IBD patients who required a prednisone prescription during 2011, did not differ among the IBD patients stratified by BMI.

There was no significant difference in rates of annual narcotic use among the IBD patients stratified by BMI.

Within our IBD cohort during 2009-2011, 56.1% of patients were treated with maintenance immunomodulators. This included 12.3% treated with methotrexate (n=184), 31.6% treated with azathioprine (n=472) and 12.2% treated with 6-MP (n=182) during the study period. Rates of immunomodulator use were similar between the IBD patients stratified by BMI during the 2009 – 2011 time periods.

In our IBD cohort 39% of patients were receiving maintenance anti-TNF therapy during the study period. This included 20.2% of the patients receiving infliximab (n=302), 15.9% treated with adalimumab (n=237) and 2.9% treated with certolizumab pegol (n=44). Between 2009-2011, there was no difference in the rates of

anti-TNF biologic use across the IBD patient subgroups stratified by BMI **(Table 2).** Additionally, no statistical difference was identified with the use of combination immunomodulator and biologic therapy in the IBD patients stratified by BMI **(Table 2).**

There was no difference in rates of ER utilization, hospitalization and IBD related surgery in the IBD patients stratified by BMI during 2011 **(Table 2).**

Polypharmacy or the number of medications used by patients may be an indirect marker of overall health status. We analyzed the total number of medications used by IBD patients during the year 2011 as well as the cumulative number of medications used during 2009 – 2011. There was a significant increase in annual and cumulative prescriptions in the IBD patients stratified by BMI **(Table 3).**

IBD maintenance therapy – weight based dosing

Although rates of anti-TNF biologic agents were similar across the IBD patients stratified by BMI, we sought to determine whether the dosages of drug actually received by subgroups of patients were similar on mg/kg basis. The current recommendation for infliximab administration is weight-based dosing starting at 5 mg/kg with dose intensification to 10mg/kg in patients who have experienced a diminished response over time. [11, 13, 22] Despite the recommendations for individualized dosing, we found a significant decrease in mg/kg dosing of infliximab as BMI increased **(Table 4).** In the class III obesity IBD patients, the average dose of infliximab was 3.96 mg/kg. The subcutaneous anti-TNF medications adalimumab and certolizumab pegol are not dosed based on patient weight, and as expected, there was a significant difference in mg/kg drug dosing

with these agents across the IBD patients stratified by BMI (p value <0.0001 for all anti-TNF biologic treatment agents).

Anti-TNF biologic agents will often require accelerated dosing, with a shortening of the treatment interval in order to maintain clinical response. We analyzed the frequency of dosing for infliximab and adalimumab in the IBD patients stratified by BMI and found no difference in the dosing frequency **(Figure 3a, 3b).**

Although no difference in the rate of immunomodulator use was seen between the IBD patients stratified by BMI, we sought to determine if the amount of drug received varied as a function of their weight. We calculated the mg/kg equivalent of the actual dose of the immunosuppressants (i.e. methotrexate, azathioprine, 6MP) and found significant differences in drug dosing between the IBD patients stratified by BMI **(Table 4).** We compared the dose of purine analog (azathioprine and 6MP) in patients receiving monotherapy and combination therapy with anti-TNF agents. We found that there was no significant difference, suggesting that dose modification in the setting of combination treatment was not influencing the dosing patterns of the immunomodulator in our cohort (data not shown).

Leukopenia can be associated with immunosuppressant maintenance medications used in the treatment of IBD and this may be related to drug dosing. To avoid this potential toxicity, white blood cell count monitoring is routinely performed in patients receiving purine analog agents. We analyzed the mean white blood cell count between 2009 - 2011 in purine analog treated IBD patients stratified by BMI and found no difference in mean levels across these subgroups **(Table 4).**

We next calculated the recommended dose of purine analogs which are typically administered with weight based dosing. We calculated the recommended dose by both body weight and IBW and compared this with the actual dosing being received by these patients stratified by BMI category. The mean daily doses of azathioprine and 6-MP per BMI subgroup are shown in **Figure 3c and 3d**. For the obese class III IBD patients to achieve recommended dosing based on actual weight, an azathioprine dose of 319.5 mg per day would be required, which was more than double the average dose which was being received (140.3 mg per day; **Figure 3c**) Weight based dosing for 6MP (1.5 mg/kg) would require 187.4 mg/kg per day in the obese class III IBD patients, again more than double the amount which was being received (92.9 mg per day as shown in **Figure 3d**).

We compared actual purine analog dosing with IBW dosing in the IBD patients stratified by BMI. The actual azathioprine and 6MP doses were similar to the calculated IBW doses for the obese IBD patients. These data suggested that IBW dosing for purine analogs was being administered to the majority of obese IBD patients.

Discussion

Previously held beliefs regarding CD and UC patients commonly being underweight are no longer accurate. In marked contrast, we found that two thirds of the IBD patients seen at our referral center are either overweight or obese. Obesity associated conditions including hypertension, diabetes mellitus and hyperlipidemia are found commonly in obese IBD patients. Weight appears to exert a negative impact on quality of life in IBD in a bimodal manner, as both underweight and obese patients had poor quality of life compared with normal or overweight individuals. BMI was associated with higher rates of CRP elevation in IBD. Interestingly, increasing BMI was not associated with increasing IBD treatment requirement or

healthcare utilization. Finally, the impact of increasing weight on IBD maintenance treatment has important ramifications as weight based dosing is not typically achieved in obese patients.

Historically, IBD predisposed patients to develop malnutrition and weight loss. A 2002 study investigating a cohort of 2065 CD patients from France found that obesity was extremely rare, occurring in 3% of individuals. [23]. This low rate of CD obesity likely reflects the year and location of the study. Obesity was less common one decade ago and France has one of the lowest rates of obesity seen in Western countries (12.9% of the French population compared with 28.5% in the U.S. according to a 2011 Organization for Economic Cooperation and Development report). The rising BMI of CD patients over the past two decades was substantiated by Moran and colleagues who investigated the patient characteristics of 10,282 individuals enrolled in 40 registry trials between the years 1991 – 2008 [42]. These authors demonstrated a significant increase in BMI for both male and female patients which were paralleled by increasing disease severity. Recent data from a multicenter pediatric IBD research consortium in the U.S. have shown that approximately one in five children with CD and one in three children with UC are overweight or obese [24]. Our data, generated from a large cohort of adult patients suggests that rates of obesity in IBD are equivalent to the general population with the majority of patients above their ideal BMI. Although our study may reflect a regional bias, the rates of obesity in Western Pennsylvania do not represent an extreme in the American population and are overall similar to trends seen throughout the U.S. at this time. [2, 3] An equally remarkable finding in our study was the identification that <2% of adult IBD patients were underweight. In fact the rate of being underweight is significantly less common than being obese (31.5% of patients with BMI $\geq$30) or super obese (i.e. obesity class III, BMI $\geq$40) which was identified in 4.4% of our cohort.

Clinical factors associated with obesity in our study included age and gender. The obese patients (obesity class II and III; i.e. BMI > 35) were older (Obese class I: 47.7 years old; Class II: 48.8 years old; Class III: 45.5 years old) and more commonly female compared to the IBD patients with normal BMI. This may be reflective of the general population who is at risk for obesity. The pediatric IBD epidemiologic investigation of obesity found an association with minority status (African American race (OR 1.64, 95% CI 1.10-2.48)) and Medicaid insurance (O.R. 1.67, 95% CI 1.19-2.34). We did not analyze ethno demographic and socioeconomic information regarding our patient population, due to the small percentage of minority patients seen in our center.

The association of obesity with worse clinical status in other chronic inflammatory conditions has remained controversial. Some of the strongest associations between obesity and a higher burden of inflammatory illness have been seen in asthma and psoriasis. The National Asthma Survey investigated the relationship between obesity and asthma severity in 3095 adult asthmatics (one third normal weight, overweight and obese) in the U.S. who provided self-reported data reflecting 5 years of symptoms and disease experience. Compared with non-overweight subjects, obese asthmatics were more likely to report continuous symptoms, miss more work days, use short acting beta agonists, use inhaled corticosteroids and use any controller medication. Obese asthmatics had significantly lower rates of asthma remission and were more likely to have persistent asthma [25]. In asthmatics, obesity was shown to be associated with worse dyspnea and wheezing over a 12 month follow-up period [17, 26, 27]. A cross sectional study of psoriatic patients followed in the Utah Psoriasis Initiative found that obesity emerged as a consequence of the psoriasis

diagnosis but no association between obesity and the emergence of psoriatic arthritis, or response to topical therapy, light based medications and systemic treatment was demonstrated. There did appear to be further synergy between obesity and other environmental factors, as a significantly higher percentage of smokers were identified who were obese. The impact of obesity on drug dosing in psoriasis outcomes has also been explored, as individuals above 100 kg showed less optimal response to fixed dose biological agents in psoriasis [16, 17, 26, 27] . Our observational study did not demonstrate a consistent signal regarding worse inflammatory burden in obese IBD patients. Although we demonstrated an association between rates of CRP elevation and BMI in IBD, this did not correlate with an increased need for treatment with steroids, immunomdulators, biologic agents or combination therapy. Interestingly, there was no difference in the rates of accelerated dosing for either weight based or fixed dose anti-TNF therapy between the normal and obese IBD patients. Finally, we were not able to explore the potential relationship between obesity as a risk factor for the development of IBD [28], as our study was a cross-sectional survey of IBD patients over a three year time period.

Obesity has risen in the U.S. population and is associated with rising health care utilization as well as increases in overall morbidity and mortality [29, 30]. Much of this increase in morbidity is linked to the concomitant rise of diseases intimately linked to obesity, specifically hypertension, diabetes mellitus and hypercholesterolemia. We demonstrated that the prevalence of hypertension, diabetes mellitus and hypercholesterolemia increased amongst IBD patients with an increasing BMI. Almost half (44.6%) of obese type III IBD patients had hypertension. This high prevalence of classic contributing factors for vascular disease suggests that the obese IBD patients will be at significant risk for coronary artery disease and stroke. . The negative impact of these metabolic syndrome defining illnesses on overall mortality is well established in

studies which were carried out in large cohorts over time periods exceeding one decade. The short observation period in our study, and the overall high rates of hospitalization and emergency department use in all subgroups of IBD patients, may have contributed to the lack of an association between BMI and increased healthcare utilization seen in our study. Investigation of BMI and the presence of metabolic syndrome co-morbidities in IBD patients followed for longer time periods will be required to better understand their interaction.

Weight reduction is the definitive approach for correcting obesity and its associated medical comorbidities. In the context of other forms of chronic inflammatory disease weight loss has been recommended as a key component in improving overall status. Weight loss, regardless of the modality, is strongly encouraged in patients with psoriasis to improve response to therapy. [26, 31] At the present time, there is limited data on weight reduction in the IBD patient population. Surgical approaches for weight reduction must be weighed extremely cautiously in IBD patients, due to the fact the either existing or future gastrointestinal tract injury will complicate IBD patients[32]. In our institutional experience, Roux en Y gastric bypass surgery in obese IBD patients was poorly tolerated and resulted in high rates of complications and subsequent hospitalization including reversal surgery [42]. More recent data suggests that a sleeve gastrectomy can be considered, although definitive information on IBD patient outcomes following this bariatric procedure is limited [33].

Obesity has important effects on immune function and homeostasis, as adipose tissue is an active source of cytokine production, including TNF-alpha, a molecule known to play a central role in IBD inflammation [34-36]. Obesity has been described as a state of systemic inflammation, and elevated CRP levels have been

previously associated with obesity in the absence of classic inflammatory and infectious etiologies [37]. Our analysis of patterns of CRP elevation in our IBD cohort showed an association between rising weight and increasing rates of CRP elevation, with the strongest association with obese class II and class III individuals (i.e. patients with BMI ≥ 35). Over half of the IBD patients with class III obesity (i.e. a BMI ≥ 40) had CRP elevation detected during a calendar year, which was markedly higher than other groups, suggesting a threshold effect of weight on CRP elevation in the absence of inflammation.

Interestingly, we found that IBD patient who were overweight (i.e. BMI 25 – 30) had some of the best patterns of overall clinical behavior identified in our study. Overweight IBD patients had the best mean quality of life scores, the lowest rates of CRP elevation, the lowest requirement for narcotics, and lower rates of hospitalization and emergency department use compared with the normal weight and obese IBD patients. This demonstration of better clinical outcomes in the overweight IBD patients as a group is in concert with recent epidemiologic studies which have demonstrated overweight body status may also be associated with better clinical outcomes in other areas. Flegal *et al*. demonstrated that all-cause mortality is lower in overweight individuals compared to normal weight population using administrative datasets. [38] Further work will be required to determine whether the IBD patient with normal or overweight status will demonstrate optimal health outcomes over time.

The relationship between obesity and worse quality of life was the strongest clinical association which emerged in our study. Although the SIBDQ is reflective of disease related quality of life, it remains unclear if this association reflects ongoing bowel disease or if it is was influenced by the negative impact of excess

weight or other comorbidities associated with obesity. The SIBDQ is known to be influenced by the presence of depression and the obese IBD patients in our cohort had higher rates of psychiatric illness compared with normal weight individuals. Obesity in itself is now recognized as a clinical factor which will negatively impact quality of life [39]. However it is important to note that underweight individuals were also noted to have low SIBDQ scores (i.e. poor quality of life). The low SIBDQ scores within this underweight sub-class have been linked specifically to active and uncontrolled disease as alternate variables that may be confounding the CRP are decreased in this population when compared to our obese patients.

One of the most important and practical issues which emerged from our study, was the challenge of drug dosing in IBD patients who are obese. Prior recommendations for immunomodulator and biologic treatment which tailor therapy to an individual patients' weight may be problematic in individuals who are markedly above their IBW. We found that the obese IBD patients were receiving dosages of medications which were overall below guidelines for actual body weight but were similar to calculated dosages targeting IBW. Our data was observational, and the treatment of these obese IBD patients was left to the clinical discretion of the treating physicians, suggesting that IBW dosing is what is frequently being administered for obese patients. This apparent reduction in drug dosing may reflect the complexity of treating individuals with multiple co-morbidities, the challenge of polypharmacy and the negative potential for drug-drug interaction, as well as the potential for impaired drug metabolism in the setting hepatic steatosis [43]. An equally intriguing finding was the lack of intensified or accelerated biologic dosing in the obese IBD patients who were receiving anti-TNF therapy with both infliximab and adalimumab. These IBD patients were dosed with equivalent frequency compared with normal weight patients, which is in marked contrast to reports from the rheumatologic and dermatologic literature. [31, 40, 41]

Our study has several important strengths and limitations. We were able to report prospective data on a large cohort of IBD patients followed over a 3 year time period. However, this population of IBD patients was recruited from a tertiary referral center, which may not be reflective of the general IBD patients seen in the U.S. In addition, our longitudinal natural history registry may suffer from ascertainment bias, as our EMR based data acquisition strategy will not capture clinical data and events outside of our hospital system. In addition, we stratified IBD patients based on patterns of laboratory findings (i.e. CRP elevation), mean quality of life scores, mean pain scores, and patterns of corticosteroid and narcotic use which are reasonable clinical markers, but have not been well validated as measures of severity in IBD clinical investigation. We chose this approach because there is no uniformly accepted IBD severity index which accurately reflects the long term burden of illness experienced by patients.

In summary, we report that one third of adult IBD patients are obese. In parallel with the rise in obese IBD patients, there has been a simultaneous disappearance of underweight patients, who are currently less common than super-obese IBD patients. Obesity exerted a negative impact on rates of CRP elevation and lowered quality of life in IBD patients, but did not increase the need for immunomodulator and biologic medications, nor did it increase rates of hospitalization and surgery in our cross sectional survey. Our findings highlight new challenges in IBD management, which include how to provide weight based dosages of medications in the setting of obesity. . The rise in obesity associated comorbidities (i.e. hypertension, diabetes mellitus and hyperlipidemia) will likely exert a negative impact on the IBD patient population over the

longterm. Further work is needed to define optimal treatment approaches for the obese IBD patient as well as approaches for healthy and successful weight loss.

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Figure legends

Figure 1:

a) BMI distribution of 1494 IBD patients. Underweight (BMI <18.5); normal weight (BMI ≥18.5 - <25); overweight (BMI ≥25 - <30); Obesity class I (BMI ≥30 - <35); obesity class II (BMI ≥ 35 - <40); obesity class III (BMI ≥ 40).

b) BMI distribution in 844 Crohn's disease (CD) patients

c) BMI distribution in 616 ulcerative colitis patients

CD obese patients (27%) vs. UC obese patients (32%). X^2(p=0.026)

Figure 2:

Rates of metabolic syndrome defining comorbidities in IBD patients stratified by BMI. Increasing BMI was associated with increasing rates of hypertenstion, diabetes mellitus and/or hyperlipidemia in IBD patients: p<0.001

Figure 3:

Dosing of biologic and purine analog agents in IBD patients stratified by BMI.

Dosing frequency of infliximab (a) and adalimumab (b) in weeks was similar for all BMI subgroups. The majority of patients (approximately 80%) receiving standard dosing of every 8 weeks for infliximab (a) and every 2 weeks for adalimumab (b).

c) Actual, recommended and ideal body weight dosing of azathioprine in IBD patients stratified by BMI. Actual and IBW dosages of azathioprine were similar in obese I, II, III subgroups, underweight, and normal weight but was significantly lower in the overweight group.

d) Actual, recommended and ideal body weight dosing of 6-MP in IBD patients stratified by BMI. Actual and IBW dosages of 6MP were similar in obese I, II, III subgroups but was significantly lower in underweight, normal and overweight groups.

TABLES

Table 1: IBD patient demographics and co-morbidities

	Under-weight (BMI <18.5)	Normal Weight (BMI ≥18.5-<25)	Overweight (BMI ≥25-<30)	Obese I (BMI ≥30-<35)	Obese II (BMI ≥35-<40)	Obese III (BMI ≥40)	p value

Number of IBD patients **(% of total IBD cohort)**	27 (1.8%)	454 (30.4%)	544 (36.4%)	276 (18.5%)	128 (8.6%)	65 (4.4%)	
Gender : number female **(% within BMI group)**	19 (70.4%)	278 (61.2%)	222 (40.8%)	122 (44.2%)	74 (58.3%)	47 (72.3%)	<0.0001
Mean age in years **(S.D in years)** **Range in years**	40.4 (13.8) (23-79)	40.1 (15.9) (17-90)	45.0 (15.1) (19-86)	47.7 (14.9) (19-85)	48.8 (13.8) (21-79)	45.5 (12.0) (23-70)	<0.0001
Hypertension: **Percentage within BMI group**		15.0%	20.0%	32.6%	36.7%	44.6%	<0.001
Diabetes mellitus: **Percentage within BMI group**		2.6%	4.0%	7.6%	14.1%	20.0%	<0.001
Hyperlipidemia: **Percentage within BMI group**		6.6%	12.3%	15.9%	21.9%	27.7%	<0.001
Coumadin treatment 2009 - 2011 **Percentage within BMI group**		3.2%	2.4%	3.2%	6.8%	3.2%	0.232
Psychiatric Co-Morbidity: N **(%within BMI group)**	8 (29.6%)	120 (26.4%)	126 (23.2%)	81 (29.3%)	47 (37.0%)	29 (44.6%)	<0.01

Table 2: IBD Activity Characteristics

	Underweight (BMI <18.5)	Normal Weight (BMI ≥18.5-<25)	Overweight (BMI ≥25-<30)	Obese I (BMI ≥30-<35)	Obese II (BMI ≥35-<40)	Obese III (BMI ≥40)	p value
Mean SIBDQ 2009-2011	45.1	51.4	52.6	50.6	48.7*	45.8*	<0.0001
Mean SIBDQ 2011	47.5	53.3	53.2	52.3	47.3*	46.8*	<0.0001
Proportions of patients with CRP elevation 2011 (% within BMI group)	36.4%	32.7%	26.2%	30.2%	37.3%	53.3%	<0.005
Proportion of patients with prednisone use 2011 (% within BMI group)	11.8%	27.9%	21.4%	21.6%	24.4%	20.9%	0.325
Proportion of patients with narcotic use 2011 (% within BMI group)	17.6%	18.8%	15.1%	16.3%	22.1%	27.9%	0.214
Maintenance immunomodulator use 2009-2011: N (% within BMI group)	17 (63.0%)	235 (51.8%)	259 (47.6%)	132 (47.8%)	58 (45.3%)	41 (63.1%)	0.086
Maintenance anti-TNF biologic use 2009-2011: N (% within BMI group)	9 (33.3%)	173 (38.1%)	196 (36.0%)	102 (37.0%)	46 (35.9%)	21 (32.3%)	0.945
Combination Therapy 2009-2011: N (% within BMI group)	5 (18.5%)	106 (23.3%)	116 (21.3%)	53 (19.2%)	25 (19.5%)	15 (23.1%)	0.803
Rates of hospitalization 2011 (% within BMI group)	17.6%	20.9%	17.5%	12.5%	19.8%	20.9%	0.501
Rates of Emergency Department use 2011 (% within BMI group)	11.8%	20.9%	16.3%	13.5%	20.9%	25.6%	0.150
Rates of IBD surgery in 2011	7.4%	7.3%	7.2%	6.0%	6.8%	8.1%	0.989

Table 3: Polypharmacy in IBD patients stratified by BMI

	Underweight (BMI <18.5)	Normal Weight (BMI ≥18.5-<25)	Overweight (BMI ≥25-<30)	Obese I (BMI ≥30-<35)	Obese II (BMI ≥35-<40)	Obese III (BMI ≥40)	F	p value
Polypharmacy 2009-2011 Mean number of medications (S.D.)	9.94 (±7.1)	10.51 (±7.9)	11.35 (±8.6)	12.46 (±9.6)	13.80 (±9.2)	16.60 (±10.9)	6.795	0.000
Polypharmacy 2011 Mean number of medications (S.D.)	5.96 (±5.9)	6.42 (±5.2)	6.27 (±5.1)	6.62 (±5.8)	7.54 (±5.9)	9.62 (±7.8)	4.294	0.001

Table 4: Actual mg/kg dosing of IBD maintenance medications in patients stratified by BMI

	Underweight (BMI <18.5)	Normal Weight (BMI ≥18.5-<25)	Overweight (BMI ≥25-<30)	Obese I (BMI ≥30-<35)	Obese II (BMI ≥35-<40)	Obese III (BMI ≥40)	p value
Weight based dose Biologic therapy mg/ kg							
Infliximab	10.74	7.89	6.38	5.41	5.36	3.96	< 0.0001
Certolizumab pegol		5.13	4.24	3.55	3.31	2.54	< 0.0001
Adalimumab	0.803	0.62	0.48	0.45	0.36	0.31	< 0.0001
Weight based dose Immunomodulator therapy mg/ kg							
Methotrexate	0.33	0.25	0.2	0.18	0.16	0.14	< 0.0001
Azathioprine	1.86	1.69	1.47	1.41	1.23	1.10	< 0.0001
6-MP	1.29	1.18	0.95	0.85	0.73	0.72	< 0.0001
Mean WBC/L 2009-2011 in purine analog treated IBD patients (S.D)	7.2 (2.759)	7.6 (2.666)	7.4 (2.775)	7.9 (2.704)	8.0 (2.242)	8.4 (2.302)	0.883

Silent Crohn's disease: Asymptomatic patients with elevated CRP are at risk for subsequent hospitalization

Short Tile: Silent Crohn's disease

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*Abbreviations***:** CD: Crohn's disease; CDAI: Crohn's Disease Activity Index; CRP: C reactive protein; EMR: electronic medical record; IBD: inflammatory bowel disease; SIBDQ: short inflammatory bowel disease questionnaire; UC: ulcerative colitis.

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ABSTRACT

Background & Aims:

Patient-reported Crohn's disease (CD) symptoms and endoscopic evaluation have historically guided routine care, but it is unknown whether patients feeling well with elevated C-reactive protein (CRP) are at risk for complications.

Methods:

This was a prospective observational study of CD patients from a tertiary care center. Subjects with short inflammatory bowel disease questionnaire (SIBDQ) scores ≥ 50 with same-day CRP measurement were eligible for inclusion. The primary outcome was disease-related hospitalizations up to 24 months after the qualifying clinic visit. We assessed the relationship between CRP and subsequent hospitalization using a chi square test, multivariable logistic regression and hospitalization-free survival analysis while adjusting for covariates.

Results:

There were 178 CD patients (mean age 42.3 years; 52.8% female) and CRP was elevated (≥0.74 mg/dL) in 24% of these individuals (n=42) who formed the "Silent CD" cohort. Mean SIBDQ and Harvey Bradshaw scores were not different between those with and without elevated CRP (58 vs. 59, P=.06; 2.9 vs. 2.04, P=.06). At 24 months, 14% (n=25) of the patients had been hospitalized for CD-related complications. The rate of hospitalization in the "Silent CD" cohort was 37% (16/42) compared to 7% of the patients without elevated CRP (9/136; P<.001). CRP elevation was associated with increased odds (OR 10.65; P<.001) of hospitalization and with an increased hazard risk of 9.48 (P<.001) on time-to-event analysis.

Conclusions:

CD patients who report good quality of life despite CRP elevation, are at a 9-fold higher risk for hospitalization over the subsequent 2 years compared to patients without a CRP elevation.

Key words: Crohn's disease; C reactive protein; disease monitoring; hospitalization.

INTRODUCTION

Crohn's disease (CD), one of the major forms of inflammatory bowel disease (IBD), is a chronic immunologically mediated disorder of the gastrointestinal tract that develops as a result of a dysregulated immune response to intestinal microflora in a genetically susceptible host.[1] The majority of CD patients experience a waxing and waning clinical course of relapse and remission. Periods of CD inflammatory activity typically correspond with symptoms, including abdominal pain, diarrhea, fatigue and elevation of the inflammatory biomarker C-reactive protein (CRP). There has been no uniform approach advocating routine use of CRP assessment in all CD patients evaluated in the outpatient setting at this time. [2]

Currently, there is no standard, structured approach to guide clinical decision making in routine CD management. No biomarker has been shown to optimally gauge CD activity (i.e. inflammation) and there is no routinely employed metric to optimally assess disease status in clinical practice. Thus, symptom based treatment with physician global assessment and periodic endoscopic evaluation have historically guided CD clinical decision-making and at present, this approach is the routine strategy used to manage the majority of patients. Symptom based treatment in CD rests on the premise that patients can accurately describe the activity of their illness, and that gastrointestinal symptoms are directly related to inflammatory activity. However, there is a growing appreciation that patient symptoms (i.e. abdominal pain, diarrhea, and fatigue) may not correlate with the activity of mucosal inflammation, and subgroups of patients may either under-report or over-report symptoms.[3] At present, there has been limited data characterizing the accuracy of patient symptoms, particularly in those patients who under-report mucosal inflammation and their longitudinal clinical ramifications.

We hypothesized that a subgroup of CD patients with elevated CRP who under-report the symptoms of their illness exist and that these individuals will be at higher risk of developing disease related complications in subsequent years compared with individuals who feel well in the absence of CRP elevation.

METHODS

Study Population

A prospectively-recruited series of IBD patients who participated in a research registry at a tertiary care center were used for this study. Inclusion criteria included adult patients with CD who were followed between the years 2009 and

2012. Prospectively collected data from clinic visits was utilized. Additional information was obtained with electronic medical record (EMR) based computer searches and manual confirmation of information.

University of Pittsburgh's Institutional Review Board approved this study (PRO12090553).

Assessment of CD clinical status

Clinical status of the CD patients was determined from the short inflammatory bowel disease questionnaire (SIBDQ) scores obtained at the time of clinic visits. The SIBDQ is a validated measure using 10 questions (each question score ranges from 1 – 7), which reflects disease-specific health-related quality of life and clinical status. [4] We used a published version where composite scores ranged from a low score of 10 (poor quality of life) to a highest score of 70 (excellent quality of life) in 10 categories reflecting bowel symptoms, systemic and social function, as well as emotional well-being.[5]

Previous analysis from our group has demonstrated that an SIBDQ score in the top third of the range (i.e. SIBDQ score 50 – 70) represents "good quality of life," and is a marker of patients doing clinically well amongst our CD population.[6] The initial SIBDQ study found a high degree of correlation between mean SIBDQ scores of 47-58 and Crohn's Disease Activity Index (CDAI) scores less than 150 (remission), the gold-standard metric for measuring disease activity.[4] Active CD was also associated with mean SIBDQ scores ranging from 40-48. Therefore, CD patients with an SIBDQ score of ≥ 50 were defined as being "asymptomatic". In a subgroup analysis, CD patients with an even higher SIBDQ score in the top quartile of the range (i.e. 55 – 70) were analyzed as a sensitivity analysis. **(Supplemental material)**

We screened the registry to identify the first clinic encounter for individual patients between 2009-2010 who had SIBDQ scores ≥50 and same-day blood draws for the inflammatory biomarker CRP[7]. CRP levels ≥ to 0.74 mg/dl were considered to be elevated and indicative of biochemical evidence of inflammation.

In addition we used demographic information, disease location according to Montreal classification[8], lifetime CD-related surgical history, Harvey-Bradshaw Index scores[9], disease duration, history of psychiatric co-morbidity and concurrent treatments.

Treatment patterns with CD medications were determined: 1) at the time of study entry (i.e. treatment at initial visit); 2) exposure during the two year follow-up time period (i.e. additional treatment). Medications were classified as immunomodulators (azathioprine, 6-mercaptopurine, and methotrexate), anti-tumor necrosis factor alpha biologic agents (infliximab, adalimumab, certolizumab pegol) and systemic steroids (i.e. prednisone). The use of narcotic treatments during the two-year study period was also analyzed.

Elevated and normal CRP CD subgroups

We divided our study population of asymptomatic CD patients (SIBDQ ≥ 50) into two groups: those with biochemical inflammation (elevated CRP) (i.e. the “Silent" CD group) and those with no biochemical inflammation (normal CRP).

Outcomes of Interest

The primary outcome of interest was CD-related hospitalizations up to 2 years after their first qualifying clinic visit. Hospitalizations due to non-CD specific reasons (i.e. trauma) were excluded from the analysis.

Statistical Analysis

Continuous variables that were normally distributed were described by their mean and standard deviation. Student’s t-test was used for significance. Median and interquartile ranges were used to describe non-parametric variables. Categorical variables were described by their frequencies and were analyzed using Pearson’s Chi-Square test. For those with expected counts less than 5, Fisher’s exact test was used.

Univariable and the stepwise selection method for constructing multivariable logistic models were used to explore the association between the binary outcome of hospitalizations and the variables CRP, disease location, lifetime history of CD-related surgery, disease duration, gender, age, and history of psychiatric co-morbidity and medication use. Uses of biologics and/or immunomodulators, as well as disease duration were included into the multivariable model to adjust for these clinically important variables.

Kaplan Meier hospitalization-free survival curves were plotted for analysis of hospitalizations up to 2 years after the index clinic visit date. Log-rank test was used to assess the difference in hospitalization-free survival between those with and without elevated CRP. The stepwise selection method was also used to construct the multivariable Cox models. Medication use and disease duration were included in the multivariable model. All tests were 2-sided with statistical significance set at $\alpha=0.05$, with the exception of the stepwise multivariable models where the significance was set at

p<0.15 for inclusion of variables in the model. Analyses were performed with STATA statistical software, version 12 (StataCorp).

Results

Study Population

There were a total of 766 CD registry patients who were followed between the years 2009 and 2012 with an initial visit between 2009 and 2010. The mean SIBDQ score from the initial clinic encounters in all CD patients over 3 years was 49 ± 13.1 SD (range 12 - 70) and the median SIBDQ score was 51. In the first clinic encounter for these CD patients, 53% (n=406) had an SIBDQ ≥ 50. Of these CD patients, 43% had a laboratory assessment including CRP performed on the same day. These 178 CD patients met our inclusion criteria and formed the study sample (mean age was 42.3 ± 14.8 years; 53% were female). The mean SIBDQ for these CD patients doing well clinically was 59 (SD 5.38). The mean Harvey-Bradshaw Index (HBI) score was 2.24 (SD 2.59). Over 85% of the patients had HBI scores $\leq$ 4, consistent with remission or inactive disease. Anatomic distribution of CD in these patients included: 29.8% ileal disease, 55.1% colonic and 44.9% ileocolonic disease. The median follow-up time for these patients was 710 days (interquartile range: 401-1011).

At the time of the initial clinic visit, 24% (n=42) of patients had elevated CRP (range 0.74-28.2 mg/dl). These 42 patients with biochemical inflammation comprised the elevated CRP group or the “Silent” CD group. The remaining 136 CD patients comprised the "Normal" CRP group.

The demographic characteristics of both groups were similar with the exception of age and disease duration. Patients with an elevated CRP (i.e. "Silent" CD) were slightly younger (38 years vs. 43 years, p=0.05) and had a shorter disease

duration (11 years vs. 15 years, P=.008). Both groups had similar overall quality of life (SIBDQ scores), HBI scores, rates of medication use and lifetime history of prior CD-related surgery. **(Table 1)**

Treatment Patterns over 24 months

At the time of study entry, treatment of patients with “Silent” CD included immunomodulator monotherapy (48%), biologic monotherapy (24%), and combination therapy (10%); 14% of patients were on narcotics and 21% on steroids. In the subsequent 2 years, biologic monotherapy decreased to 17%, and immunomodulators monotherapy to 45%, while combination therapy rose to 21%. There was an overall increase in narcotic and steroid exposure to 19% and 31%, respectively.

Baseline treatment in the "Normal" CRP cohort included 20% on biologic monotherapy, 43% on immunomodulator monotherapy and 15% on combination therapy. At study entry, 15% were on steroids and 11% on narcotics. After 2 years, biologic and immunomodulator monotherapy remained relatively unchanged at 21% and 42%, respectively, while combination therapy was used by 20%. Narcotic and steroid use increased, with 18% exposed to steroids and 14% to narcotics. Overall, there was no difference in the rates of medications at baseline or during follow up between the “Silent” CD and "Normal" CRP groups.

Unadjusted outcomes

Over the two-year period, 14% (n=25) of the patients were hospitalized. This included 7% of the "Normal" CRP group versus 37% of the “Silent” CD cohort (P<.001). On univariable logistic regression, “Silent” CD patients were significantly more likely to experience hospitalizations compared to those with normal CRP (unadjusted odds ratio (UOR) 8.68; 95% CI 3.46-21.77; P<.001). In addition, those with steroid exposure were significantly more likely to be hospitalized as well (UOR 3.66; 95% CI, 1.26-7.2; P=.013). There was no significant decrease in the likelihood of hospitalization between patients on biologics, immunomodulators or combination therapy. **(Table 2)**

Adjusted outcomes

In the multivariable model, while adjusting for IBD-related medications and disease duration, the presence of an elevated CRP, steroid use and history of psychiatric co-morbid illnesses were significant predictors of hospitalization. Elevated CRP was associated with 10 times the odds of hospitalization (adjusted odds ratio (AOR) 10.65; 95% CI 3.69-30.64; P<.001). Steroid use was associated with 4 times the odds (AOR 4.22; 95% CI 1.44-10.29; P=.009) and history of psychiatric co-morbidity was associated with 3 times the odds of hospitalization (AOR 3.26; 95% CI 1.01-10.47; P=.047). **(Table 3)**

Time to event analysis

In a Kaplan-Meier analysis, elevated CRP was associated with an increased incidence of hospitalization at 2 years for patients with SIBDQ ≥ 50 (P log rank=.0001) **(Figure 1)**. The median time to event in the "Silent" CD group was 175 days, compared to 412 days in the "Normal" CRP group. On univariable (unadjusted) Cox regression analysis, elevated CRP was associated with a 7.53 hazard ratio (HR) of hospitalization (Unadjusted Hazard Ratio (UHR) 7.53; 95% CI 3.31-17.09; P<.001). Steroid use was associated with a 3.2 fold HR of hospitalization (UHR 3.2; 95% CI 1.45-7.05; P=.004). **(Table 4)**

In the multivariable Cox model, while adjusting for medications and disease duration, CRP was independently associated with 9.48 times the HR of hospitalization (Adjusted Hazard Ratio (AHR) 9.48; 95% CI 3.75-24; P<.001) as well as steroid use (AHR 3.21; 95% CI 1.32-7.8; P=.010). Male gender was also independently associated with 2.72 times the HR of hospitalization compared to females (AHR 2.72; 95% CI: 1.14-6.52; P=.025). **(Table 5)**

Hospitalizations

In the "Silent" CD group, the majority of the hospitalizations (n=16) were for intestinal resections (7/16). The remainder of the hospitalizations where for: management of abscesses (2/16), fistulas (2/16), dehydration (2/16), CD flare-ups (1/16), drug-induced pancreatitis (1/16), and small bowel obstruction (1/16). In the "Normal" CRP group, the hospitalizations were due to intestinal resections (5/9), fistulas (1/9), abscesses (1/9), CD flare-ups (1/9), and small bowel obstruction (1/9).

The hospitalizations that were not included in the analysis were those related to pneumonias, chest pain episodes, pre-syncope, cholecystectomy, spine surgery, and post-endoscopic retrograde cholangiopancreatography related pancreatitis.

Discussion

In this prospective analysis of CD patients followed longitudinally in an outpatient setting employing routine metrics to gauge clinical status and biochemical presence of inflammation, we have identified that: 1) there is a subgroup of CD patients who under-report inflammatory activity (i.e. have an elevated CRP) and have similar symptoms to CD patients feeling well with no elevation in CRP; 2) these “Silent" CD patients represent up to one quarter of CD individuals who are in clinical remission in a tertiary referral setting; 3) "Silent" CD patients are at increased risk of experiencing complications over the subsequent 2 years, with 37% requiring CD-related hospitalizations compared to 7% of patients who felt well and had a normal CRP; 4) routine metrics of clinical status, specifically the SIBDQ and the HBI were readily implemented in the clinic and our study demonstrates feasibility of this approach; 5) SIBDQ and HBI provide structure to assist in the routine outpatient management of CD patients and these metrics aided in the identification of patient subgroups further stratified by objective measures of inflammation (i.e. CRP).

The classic paradigm for CD outpatient care has emphasized symptom based therapy, and this treatment strategy is based on the assumption that patients are able to accurately describe their symptoms which are thought to be linked to the level of inflammatory activity. However, recent investigation has identified a discrepancy, where many patients suffering from abdominal symptoms are in fact experiencing functional symptoms in the absence of objective inflammatory activity rather than pain due to CD inflammation. This concept has been labeled “irritable bowel syndrome (IBS) in IBD” and may result from factors including surgically altered anatomy, bile acid diarrhea, nerve injury and/or altered intestinal physiology. In a recent evaluation of new immunosuppressive therapy, 18% of CD patients who met inclusion criteria (i.e. abdominal symptoms, poor overall wellbeing, diarrhea, etc.) had no objective evidence of inflammation on endoscopic assessment.[3] We evaluated the converse, focusing on the subgroup of asymptomatic CD patients who feel well despite objective evidence of inflammation.

This concept of “Silent” disease, where subgroups of patients have limited symptomatology compared with the majority of patients is well established in other areas of medicine, including cardiology. “Silent ischemia” was identified in a subset of patients with ischemic heart disease[12] who fail to complain of anginal symptoms but are at increased risk of cardiac events over the ensuing months/years.[13] Diabetic patients represent a subgroup of ischemic heart disease patients who are classically known to have limited or diminished symptomatology, warranting investigation/intervention

in the absence of classic angina symptoms. We have identified a parallel finding in a subset of CD patients who feel clinically well, despite having objective, biochemical evidence of inflammation, with important health consequences which emerge in the next 1-2 years.

An important aspect of our study involved monitoring CD patients in an office setting with routinely-employed disease activity metrics (SIBDQ and HBI) and laboratory markers (CRP) to gauge clinical disease and inflammatory activity. The use of standard health related quality of life measures and disease activity metrics to provide a structure for the analysis of CD clinical status in the routine office setting, as opposed to a clinical trial, has been limited to referral centers. We chose two measures of disease status, the SIBDQ and the HBI in addition to standard laboratories to identify subgroups of patients who are at increased risk for complications.[10] The 10-item SIBDQ questionnaire proved to be easily administered in the outpatient setting in contrast with the CDAI, which requires a week-long patient diary making it more cumbersome and impractical for use in a clinic setting.[11]

There have been numerous studies investigating the ability of CRP to gauge clinical status in CD. Elevation in CRP has been used as a filter in the recruitment of CD patients for randomized controlled trials to ensure that these patients had objective evidence of inflammation and were not suffering from functional symptoms.[15] In the context of predicting the natural course of CD, the majority of studies have demonstrated utility of CRP in predicting clinical relapse [21]. Early studies investigating CRP in CD identified similar rates of elevation in asymptomatic patients (up to 1/3 of the patients).[14] These investigators found that quiescent patients with CRP elevation were at increased risk for clinical relapse in the next 1-2 years. Our study identified similar rates of asymptomatic CD patients with elevated CRP, but our findings suggest increased risk in the next 6 months on Kaplan-Meier analysis **(Figure 1)**.

The sensitivity of CRP in demonstrating CD inflammation has been evaluated, and compared with other objective modalities, including endoscopy, radiology and disease activity indices. Current data suggest that CRP is less sensitive than endoscopy, and will elevate when there is more significant inflammation in the mucosa. Fecal calprotectin has emerged as a clinically useful fecal biomarker for predicting relapse, which is more sensitive than CRP, but it has also been found to correlate poorly with CDAI. Therefore, an elevation in CRP, despite patients being asymptomatic, may be even more important clinically, as this implies a more advanced elevation in inflammation compared with the elevated fecal biomarker. Finally, economic factors will also influence the practical use of objective markers of CD inflammation, as fecal calprotectin is three times more expensive than high sensitivity CRP ($230 vs. $80; Quest Diagnostics) in the US at the present time.

Our study has several important strengths and limitations. Our use of a prospective registry based in a routine clinic did not mandate regimented monitoring at specific time points, and likewise, treatment decisions were not structured. Therefore, the data generated from this analysis is not as straightforward as a clinical trial with predetermined treatment schedules and endpoints. However, our data reflects real-world challenges regarding routine clinical care of

CD patients. Although randomized controlled clinical trials are an ideal structure for defining clinical information, they may not be reflective of real world clinical management. Indeed, all of the patients evaluated in this study would have been felt to be in clinical remission using a CDAI score (reflecting well being, diarrhea, and abdominal pain). The Institute of Medicine has recently advocated for clinical investigation to place more emphasis on observational trials that yield widely applicable results, to generate data that helps to inform decision making in routine clinical care.[19-20] Therefore, future IBD research involving disease monitoring may benefit more from similar approaches which emphasize the use of standard metrics in the clinic as a next wave of comparativeness effectiveness research supplements data from randomized clinical trials.

There were limitations in our study. Smoking history was not ascertained. Tobacco is known to be an important environmental factor which negatively impacts the clinical course of CD. Another important limitation to our study included the lack of endoscopic or imaging studies to confirm the inflammatory activity, as the majority of CD patients were deemed to be in clinical remission. There were a substantial number of CD patients with good SIBDQ scores who did not have CRP levels available for review (56% of patients feeling well at the first clinic encounter reviewed). However, 21% of these CD patients who did not have CRP tested during the index clinic visit required hospitalization over the next two years, which was similar to the rates in the study population. Finally, fecal calprotectin might be useful in assessing CD activity, but this assay was not routinely available in our clinic at the time of this study

In conclusion, symptom-based treatment paradigms may fail to identify CD patients at risk for complications. CD patients who are clinically well yet exhibit elevated CRP levels, “Silent” CD patients, are at risk for hospitalization in the ensuing 1-2 years. Our exploratory analysis supports a role for routinely checking inflammatory markers in CD patients during routine management. What remains unknown is whether additional diagnostic evaluation and treatment modification would change clinical outcomes. The routine use of disease activity metrics, objective markers of inflammation in combination with patient symptoms and global assessment may better help identify patients at risk for poor clinical outcomes. Overall, the use of a structured clinic evaluation with objective metrics will facilitate identification of patient subgroups and the implementation of a personalized approach for CD management.

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FIGURE LEGENDS:

Figure 1: Kaplan-Meier Curve of time to hospitalization in CD patients evaluated in clinic with SIBDQ scores $\geq$ 50, stratified by normal and elevated CRP levels. Median time to event was 175 days in the elevated CRP group vs. 412 days in the normal CRP group.

TABLES:

Table 1. Baseline Demographics and Clinical Characteristics

SIBDQ ≥50				
		Total (N=178)	**Elevated CRP (N=42)**	**Normal CRP (N=136**
Age, mean (SD)		42.3(±14.8)	38.3(±14.4)	43.5(±14.8)
% Gender	**Female**	52.80	52.40	52.90
	Male	47.20	47.60	47.10
% Disease Location	**Ileal (L1)**	29.78	19.05	33.09
	Colonic (L2)	55.06	28.57	24.26
	Ileocolonic (L3)	44.94	52.38	42.65

% History of Psychiatric Co morbidity		19.66	19.05	19.85
% History of Surgery		45.51	38.10	47.80
Disease Duration* in years (SD)		14(10.6)	10.3(8.8)	15(11)
Mean SIBDQ (SD)		59(5.38)	57.6(5.6)	59.4(5.25)
Harvey Bradshaw Index Scores (SD)		2.2(2.6)	2.9(3)	2(2.4)
% Rates of Medications	**Biologics**	40	38	40
	Immunomodulators	63	67	62
	Narcotics	15	19	14
	Steroids	21	31	18

Baseline demographics and clinical characteristics of CD patients with SIBDQ ≥50. Elevated CRP patients were younger and had shorter disease duration.

Table 2: Univariable Logistic Regression

SIBDQ Score ≥50 (N=178)				
		(UOR)	P-value	95% CI
Elevated CRP		8.68	**<.001**	3.4-21.77
Male Gender		1.83	.171	0.77-4.32
Age		0.98	.362	0.95-1.01
Disease Location	**Ileal (L1)**	*	*	*
	Colonic (L2)	1.01	.985	.313-3.26
	Ileocolonic (L3)	1.15	.773	.42-3.16
History of Surgery		0.93	.87	0.39-2.18
Disease Duration		0.99	.583	0.95-1.03
History of Psychiatric Co morbidity		1.74	.262	0.66-4.55
Medications	**Biologics**	0.67	.387	0.27-1.65
	Immunomodulators	2.04	.15	0.77-5.40
	Narcotics	2.58	.06	0.95-6.97
	Steroids	3.66	**.004**	1.50-8.95

Univariable logistic regression for CD patients with SIBDQ ≥50. Elevated CRP and steroids were significantly associated with hospitalizations. Narcotics were approaching significance.

Table 3: Multivariable Logistic Regression

SIBDQ Score ≥50 (N=178)			
	Adjusted Odds Ratio	**P-value**	**95% CI**

Elevated CRP	10.65	**<.001**	3.69-30.64
Steroids	4.22	**.009**	1.44-10.29
History of Psychiatric Co morbidity	3.26	**.047**	1.01-10.47
Biologics	0.69	.502	0.24-2.01
Immunomodulators	1.57	.433	0.51-4.80
Disease Duration	1.02	.278	0.97-1.07
Male Gender	2.30	.107	0.83-6.32

Multivariable logistic regression for CD patients with SIBDQ ≥50. Elevated CRP, steroids and history of psychiatric co morbidity were significantly associated with hospitalization, while adjusting for medications and disease duration.

Table 4: Univariable Cox Regression

SIBDQ Score ≥ 50 (N=178)				
		Hazard Ratio	**P - value**	**95% CI**
Elevated CRP		7.53	**<.001**	3.32-17.09
Male Gender		1.8	.148	0.81-4.02
Age		0.98	.365	0.96-1.01
Disease Location	**Ileal (L1)**	*	*	*
	Colonic (L2)	0.95	.923	.318-2.82
	Ileocolonic (L3)	1.16	.748	.45-2.96
History of Surgery		0.90	.812	0.41-2.00
History of Psychiatric Co morbidity		1.53	.345	0.64-3.64

Biologics	0.66	.34	0.29-1.53
Immunomodulators	1.90	.170	0.76-4.76
Narcotics	2.24	.07	0.94-5.36
Steroids	3.2	**.004**	1.45-7.05
Disease Duration	0.99	.635	0.96-1.03

Univariable Cox Regression for CD patients with SIBDQ ≥50. Elevated CRP and Steroids were significantly associated with hospitalizations.

Table 5: Multivariable Cox Regression

SIBDQ Score≥50 (N=178)			
	Adjusted Hazard Ratio	**P-value**	**95% CI**
Elevated CRP	9.48	**<.001**	3.75-24
Steroids	3.21	**.01**	1.32-7.8
Male Gender	2.72	**.025**	1.14-6.52
History of Psychiatric Co morbidity	2.52	.07	0.92-6.96
Biologics	0.63	.331	0.25-1.6
Immunomodulators	1.28	.619	0.49-3.37
Disease Duration	1.04	.99	0.99-1.08

Multivariable Cox Regression for CD patients with SIBDQ ≥50. Elevated CRP, steroids and male gender were significantly associated with hospitalization, while adjusting for medications and disease duration.