

Study Protocol

The Trend of National and Sub-national Burden of Gastrointestinal and Liver Diseases in Iran 1990 to 2013; Study Protocol

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Abstract

Background: It is expected that gastrointestinal (GI) and liver diseases inflict considerable burden on health systems in Iran; therefore, highlighting the significance of GI disorders across the other most burdensome diseases requires comprehensive assessment and regular updates of the statistics of such diseases in Iran.

Objective: To assess in-depth sub-national estimates and trends for the incidence and prevalence of selected GI and liver diseases by age, gender and province over the period 1990 – 2013 in Iran.

Methods: This is a national and sub-national burden of disease study on 21 GI diseases using all available data sources, including cancer registry, death registration system data, hospital data, and all available published data. Analyses will be performed separately by gender, age groups, year, and province. We will conduct 21 separated systematic reviews of the literature for 21 diseases categories through searching online international electronic databases (i.e. the Medline database of the National Library of Medicine, Web of Science, and Scopus), Iranian search engines (i.e., IranMedex, Scientific Information Database (SID), and IRANDOC), and gray literature. We will search the medical literature published between January 1985 and December 2013. We generated two models, Spatio-temporal and Multilevel Autoregressive models, to estimate mean and uncertainty interval for the parameters of interest by gender, age, year, and province. The models will be informed by data of gender, age, year, and province. Markov Chain Monte Carlo (MCMC) methods will be used to perform Bayesian inference in both modeling framework. All programs will be written in R statistical packages (version 3.0.1).

Results: We will calculate and present 1990 to 2013 trends in terms of prevalence, years of life lost due to premature mortality (YLLs), years lived with disability (YLDs), and disability-adjusted life years DALYs for the 21 selected GI diseases by gender, and province. We will also quantify the uncertainty interval for the estimates of interest.

Conclusion: Results of the present study will have implications for policy making; as they allow for understanding geographic distributions of the selected GI diseases, and identifying health disparities across provinces.

Keywords: Burden of illness, costs of disease, illness Burden

Cite this article as: Salimzadeh H, Ardeshtir Larijani F, Abedian Sh, Kalantar Motamedi SM, Malekzadeh MM, Mohaghegh H, et al. The trend of national and sub-national burden of gastrointestinal and liver diseases in Iran 1990 to 2013; study protocol. *Arch Iran Med.* 2014; **17(1)**: 33 – 53.

Introduction

Non communicable diseases including digestive diseases are the cause of almost two-third of deaths worldwide accounting for 54 % of global disability-adjusted life years (DALYs).¹⁻² In 2010, digestive diseases and cirrhosis contributed

to roughly 2.6 % of the global DALYs reflecting a notable share in health loss particularly in developed and high-income countries.²⁻⁴ All ages mortality from most gastrointestinal (GI) diseases have slightly changed in the past two decades, but a significant increase (12 %) has been reported for cirrhosis and peptic ulcer which have showed a remarkable decrease, falling by 29 % from 1990 to 2010.² It is expected that GI diseases inflict considerable burden on health systems in Iran⁵ where cardiovascular disease, injuries and cancers are considered as more important from a health policy perspective⁶ According to recent statistics, digestive diseases in Iran accounted for approximately 1.2 % of all ages DALYs in 2010, of which near a third were due to cirrhosis.² However, highlighting the significance of GI disorders across the other most burdensome diseases requires comprehensive assessment and regular updates of the statistics of such diseases in Iran.

Many countries have characterized local patterns of diseases through national and sub-national burden of diseases studies.⁷⁻¹² The study of burden of diseases was also conducted in Iran in 2003 and provided national estimates on the burden of more than 200 diseases and causes of injuries, and 27 selected risk factors.⁶

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Accepted for publication: 3 December 2013

In practice, part of health policies are mostly made and implemented at provincial or even district levels, reflecting the significance of contextualized evidence for allocation of resources to health systems, as well as for identifying health disparities across provinces.^{7-8,10} Nonetheless, all estimates of the previous burden of disease study for Iran are representative only at national level and therefore the applicability of the results in local conditions is under question.

Drawing from the experiences learned through the 2003 study, the National and Sub-national Burden of Diseases (NASBOD) study was designed as the first effort to provide national and sub-national estimates for burden of diseases in Iran over the past two decades. Given the availability of high quality sub-national data and updated analytic methods, the NASBOD study will provide a chance both to assess in-depth sub-national estimates and trends in epidemiological parameters of diseases over the period 1990 – 2013 in Iran. The key differences between the NASBOD study and the previous study include definitions, scope and coverage of the study, age groups, diseases and risk factors included in the study, data sources, methods, and analyses which are discussed somewhere else.¹³

The study of national and sub-national burden of GI diseases from 1990 – 2013 in Iran is a part of the NASBOD study and aims to provide quantitative and valid estimates for the incidence and prevalence of selected gastrointestinal and liver diseases by age, gender and province from 1990 to 2013. In this article, we describe definitions, data sources and methods in general. Disease-specific articles will be prepared explaining data, methods, and results for that specific disease in detail.

Materials and Methods

Overview

This is a national and sub-national burden of disease study on 21 GI diseases using all available data sources, including cancer registry, death registration system data, hospital data, and all available published data. We will estimate 1990 to 2013 trends in terms of prevalence, years of life lost due to premature mortality (YLLs), years lived with disability (YLDs), and DALYs of the selected GI diseases by gender, and province. We will also quantify the uncertainty associated with the estimates of interest. Analyses will be performed separately by gender, age groups, year, and province.

Organizing working groups

In order to receive inputs from key stakeholders, we put emphasis on participation of national and international experts in the fields of gastroenterology, health research, clinical care, pathology, public health, epidemiology, and health economics. In principal, in this study we constituted a core committee and several technical advisory groups represented as our working groups. The working groups will guide overall project and have an important role in providing advice on the selection of diseases, disease definition, identifying data sources, modeling methods, interpretation of the findings, and publication strategy. It is essential that the members of working groups acquire an optimum level of knowledge on the burden of diseases study methods. In order to ensure this, we will administer a number of workshops with the involvement of all levels of expertise covering subjects that make estimates consistent across individuals in the working group.

Disease selection process

In the current study gastrointestinal and liver diseases have been initially selected based on the list used for the Global Burden of Disease (GBD) 2010.² Since some of the diseases which are not included in the GBD list are locally important, we modified the GBD list to become adjusted to our country's health profile. To start disease selection process, we relied on the national pattern of cause of death, the World Health Organization (WHO) report on non-communicable diseases, and GLOBOCAN estimates of cancer death for Iran.^{1,5,14} The primary list included 37 disease categories which required further modifications using disease selection criteria including severity, prevalence (from surveys), incidence (from disease registries), clinical judgment, and data availability. Furthermore, some important diseases, such as celiac disease,¹⁵⁻¹⁶ and fatty liver were added to the GBD list because of the availability of relevant data and their economic burden relative to others.¹⁷

In order to receive specific guidance and feedbacks from more involved experts, the primary list was circulated to the members of the Iranian Association of Gastroenterology and Hepatology (IAGH) and the experts of Digestive Disease Research Institute (DDRI) affiliated to Tehran University of Medical Sciences to weight diseases according to above mentioned selection criteria. We finally provided a condensed list of 21 categories of digestive and liver diseases incorporating core committee suggestions and the inputs of IAGH and DDRI experts.

Clinical vs. practical definition of selected GI diseases

For each disease we chose the most appropriate practical definition focusing on data availability rather than disease diagnostic criteria. This means that definition used for selected diseases include one or more evidences from pathologic reports, clinical information, sonography information, endoscopic, or laboratory findings. For example the definition of duodenal ulcer is based on endoscopic and hospital data, and the definition of cirrhosis is based on clinicopathological and radiological findings. However, definitions of some diseases such as gastro esophageal reflux disease (GERD) or irritable bowel syndrome (IBS) are based on international criteria, such as ROME criteria.¹⁸ In these definitions we also considered the availability of data, clinical judgment and their economic burden on health. For example, in cirrhosis we included only decompensated form of cirrhosis because the burden of cirrhosis is mostly from the decompensated cirrhosis, and patients in compensated state are usually asymptomatic, with no significant burden.¹⁹ More details about the definition of the selected digestive diseases and the respective ICD-10 codes (the 10th version of the International Classification of Diseases) for each disease are presented in Table 1 (See Table 1).²⁰

Data sources

In order to make the database as complete as possible and to extract the data from all available data sources, we will use a systematic approach to accomplish this study. Prevalence and incidence estimates for the selected GI diseases will be calculated using available national databases as well as systematic reviews of the national literature. While, the availability of data sources is likely to vary across different provinces, we generally identified and documented a number of data sources related to the selected digestive diseases. The following sections of this paper provide explanatory details on data sources included in this study.

Systematic reviews

We will conduct 21 separated systematic reviews of the literature for 21 diseases categories through searching online international electronic databases (i.e. the Medline database of the National Library of Medicine, Web of Science, and Scopus), Iranian search engines (i.e., IranMedex, Scientific Information Database (SID), and IRANDOC), and gray literature.

Search strategy

We will search the medical literature published between January 1985 and December 2013 using Medline (PubMed), Web of Science, Scopus, and the Iranian digital databases. This means that we will search the databases for papers with any of the search terms of interest in the title or abstract. The medical subject headings (MeSH) of PubMed (and also entry terms or synonyms) and Emtree will be used for extracting search terms from international electronic databases. More details on our search strategy and search terms used for GI diseases can be found in appendix A (See Appendix A). Our searches will be limited to a given time period (published between 1985 and 2013), to Iran, to human subjects with no language restriction.

With respect to Iranian databases, we will search all abstracts, conference proceeding, titles of thesis, dissertations, and reports that are published in Persian and indexed in IranMedex, SID, and IRANDOC; the Persian search terms are equivalent to their English search term. Additionally, gray literature such as the Ministry of Health and Medical Education (MOHME) reports, and booklets, which are not appeared in the domestic electronic databases, will be searched through contacting authors or experts. In order to ensure that all experts will deeply and consistently search relevant concepts, we developed search flowcharts for PubMed and domestic search engines. These flowcharts illustrate certain aspects of search (e.g., different spelling of Persian terms, indexing limitations in domestic search engines) as well as steps required to have more comprehensive and concise search results. In principle, the flowcharts complement the search process as they address problems that arise particularly when working with domestic search engines (See Appendix B).

Study selection criteria

Articles and grey literature published in English in the period 1985 to 2013 will be included in the systematic reviews. Generally, all papers that reported any relevant data on disease parameters (incidence, and prevalence) from population-based or cross-sectional studies, disease registry, and hospital-based surveys are potentially eligible for the systematic reviews. We will retrieve relevant articles from the databases and after removing duplicate papers they will be passed to the next level. In the next stage, two reviewers will independently screen all titles (first step), abstracts (second step), and full-text of the studies (third step). In order to maximize the sensitivity of our search, reference lists of the selected full-text articles will be screened for titles that included search terms. Full-text of selected articles will be critically appraised independently by two well-trained reviewers using a simple checklist (See Appendix C), and disagreements between the reviewers about eligibility will be resolved through discussion.

Data extraction

In this stage, data from eligible full text articles will be extracted and entered into electronic spreadsheets independently by two

researchers. The discrepancy between researchers on the data will be resolved through consensus. Authors of articles that have not presented the required data will be contacted for provision of needed information. Given the various methods of different identified studies (objectives, methods, and settings), we will incorporate needed information in a spreadsheet that contains the following items:

- General information: Study name, citation, city (where the study was conducted), publication year, study year, journal, characteristics and contact address of corresponding author.
- Population characteristics: Age (age groups as: 0 – 4, 5 – 9, 10 – 19, 20 – 29, 30 – 39, 40 – 49, 50 – 59, 60 – 69, 70 – 79, 80+), gender.
- Methodological information: Study design, data source, scope of study (urban or rural), coverage of the study (national, provincial, district, and community level), measurement tools, sample size, sampling method, sample weight, response rate.
- Study outcomes: Proportion of cases to the total number of population included in the study (prevalence), incidence, mortality - all presented with 95 % uncertainty interval and stratified by gender and age groups.

Other sources (existing databases)

Cancer registry

Briefly, cancer registration is a procedure in which cancer reports are collected, registered and analyzed continuously and carefully by MOHME. Indeed, National Cancer Registry (NCR) in Iran was pathology based however it has become population based in recent years (e.g. therapy, imaging, death certificates, hospital data, private clinics, etc.). The guidelines for utilization of hospital medical files as well as morbidity and mortality records in pilot provinces have been formulated and distributed among the involved units since 2005. Since all sites of cancer such as pancreas are not routinely biopsied, several studies have shown that in optimal conditions of cancer registration based on pathology reports, a maximum of 80 % of cancer cases may be registered.²¹ Moreover, in some cancer cases such as advanced hepatocellular carcinoma, diagnosed based on radiological or endoscopic findings, it may not be ethical to take biopsy samples, therefore these cases are not reported to cancer registry. Differentiation between metastatic tumours and those that originate from GI tract is another concern of cancer registries. Therefore, the cancer registry data need more evaluation regarding completeness and misclassification of data collected from all over the country and all cancer sites.

Death registry

Accurate and complete cause-specific mortality data is one of the most informative sources to estimate the extent of diseases epidemic.²² Yet death registration is facing the problems of misclassification and incompleteness in many countries.¹ Death registration system in Iran is sponsored by MOHME and captures about 86 % of all deaths occurring in the country.²³ A systematic review of 31 studies on burden of disease conducted on the global or country level from 1990 to 2011 showed that only 10 studies addressed the underreporting of death statistics.²⁴ Nevertheless, we will deal with accurate coding of cause-specific mortality as well as the incompleteness of death registry.

Primary data (field data)

Data gathering for some outpatient diseases such as inflamma-

tory bowel disease (IBD) will be based on office-based physicians (gastroenterologists) visits. As the first step, we will use IAGH members list to extract the contact information of gastroenterologists who are managing these patients all over the country. In the next step, an invitation will be sent to them enclosing a questionnaire. Finally, the physicians and gastroenterology clinics throughout the country will be invited again via telephone call or e-mail. Indeed these physicians will be asked to prepare needed data through completing data collection forms using their clinics' records. However, the collected data will not reflect under diagnosed and under treated patients who suffer from these diseases.

Hospital data

We will utilize hospital discharge data as an important source of information about acute events such as appendicitis as well as chronic diseases like cirrhosis. In this data source we should deal with some concerns about selection bias, and variations of patients in terms of access to hospital care. More details on hospital registries' data are described elsewhere.²⁵

Datasets of Iranian Blood Transfusion Organization (IBTO)

The data about hepatitis B and hepatitis C in blood donors, and also the information about volunteers rejected from blood donation will be retrieved from the IBTO dataset.

Endoscopic data

To compute the prevalence of some diseases we can assess the utilization and indications of endoscopic procedures using the data of health insurance organizations.

Cohort studies

We will collect data on remission rates, duration, and mortality risks for some events such as gastric cancer from cohort studies of Golestan and Ardebil.²⁶

National Rational Drug Prescription database

We will characterize prevalence of some diseases based on disease-specific rates of drug use. This proxy indicator is estimated using the National Rational Drug Prescription information.

Statistical methods and analysis plans

Despite our extensive search and access to all national surveys, there will be many provinces without data or without provincial representative data. Moreover, results of many surveys do not cover all age groups, both genders, and or both rural and urban areas of residency. We generated two distinct statistical models (i.e., spatio-temporal and multilevel autoregressive models) to estimate mean and uncertainty interval for the parameters of interest by gender, age, year, and province. We are using two models to make sure that there is no model dependency in the results. The models will be informed using data about gender, age, year, and province. For the provinces, which have been separated from other provinces in the desired period of time, we face the problem of misaligned areal units. The problem is going to be addressed in both models. In addition, we will deal with different classification of data reported as summary statistics by cross walking between continuous and categorical values of variables of interest using regression models. Specific features of models are briefly described as follows.

Spatio-temporal model

We will apply Spatio-temporal Bayesian hierarchical modeling with conditional autoregressive prior for spatial random effects.²⁷ In spatial framework observations which are closer in space are assumed to be more correlated than observations farther away. This structure enables model to 'borrow information' from neighbouring areal units to improve estimates for areas with missing values and/or small number of observations. In addition, we will combine incompatible areal units between data sources and/or over the years using spatio-temporal misalignment modeling. The model includes covariates effects, non-linear age trend, and variations in study quality and source of data.

Bayesian Multilevel Autoregressive model

In this framework, observations are hierarchically nested in districts, provinces, sub-regions, regions, and national levels, respectively.²⁸ In the hierarchical model, higher levels borrow information to the lower levels and units of each level borrow information to each other depending on the degree of data availability. The model addresses several different components including linear time trends, nonlinear changes over time, covariate effects, nonlinearity associated with age, heterogeneity of data sources, and age-by-study variability. Time-varying district-level or province-level covariates inform the estimates if practical.

Because of general applicability and ease of implementation of the Markov Chain Monte Carlo (MCMC) methods, we will use these methods to perform Bayesian inference in both modeling frameworks. All programs will be written in R statistical packages (version 3.0.1).

Discussion

Despite the substantial burden of GI disease, there is no sufficient infrastructure and resource in MOHME for health policy view in this field in Iran. Compared with heart diseases, cancer, and HIV, GI diseases, as a major part of diseases, have not received the necessary support from health policy makers. Likewise, the health burden of GI diseases is overlooked by MOHME with respect to appropriate funding for clinical research and service delivery at both primary and secondary levels. The absence of an independent office for gastroenterology and hepatology in MOHME affirms this conclusion. Future national plans to control GI diseases are dependent to a large extent upon highlighting the significance of GI diseases from a public health perspective. Fortunately, our study will represent informative data relating to most areas of GI diseases, and hence can provide a great body of evidence which could be used appropriately by IAGH physicians and policy makers to lobby for service delivery and research funding.

At the global level, although all ages DALYs for digestive diseases (except cirrhosis and cancers) have declined by 2.6 % from 1990 to 2010, cirrhosis, liver cancer, stomach cancer, and colon and rectum cancers appeared in the top ten diseases in at least one region of the world. Indeed, in 2010 the share of DALYs from liver cancer and pancreatic cancer increased the most among the top cancer causes in the world; in addition, the global DALYs of colon and rectum cancers exceeded 35 % from 1990 to 2010.²

In 2003, digestive system diseases (excluding neoplasm) were the seventh leading cause of burden among the most burdensome disease groups in Iran;⁶ however, the burden of GI diseases is likely to increase steadily because of epidemiological transitions

and shifts in age-structure to elder population in Iran since 2003. The GBD 2010 estimates for Iran show a downward trend in the magnitude of DALYs since 1990 which is due to this group of diseases.² The story is more complicated when we compare Iran with other regional counterparts. Whereas all ages YLLs for liver cancer, pancreatic cancer, and colorectal cancer has increased in countries such as Oman, Kuwait, Qatar, and Turkey, gastric cancer was the only GI cancer to be appeared in the list of top YLLs causes for Iran in GBD 2010. The results imply that the burden caused by these neoplasms in Iran is lower than that in the mentioned regions. However, it seems that the same set of factors that account for GI cancers in Iran could also occur in Oman, Kuwait, Qatar, and Turkey.

Cirrhosis was the other GI event to be included in the list of top YLLs causes for Iran in GBD 2010. In fact, 0.4 % of total DALYs were due to cirrhosis, of which approximately a third were caused by hepatitis C and nearly equal share were related to hepatitis B, and alcohol use.² These results are worth noting particularly with respect to the aetiology of cirrhosis in Iran. Surprisingly, hepatitis B, the most common cause of cirrhosis in Iran, accounted for only 0.07 % of total DALYs of cirrhosis.¹⁹ Although the actual burden of cirrhosis remains still unknown in Iran, the lower DALYs of cirrhosis reported for Iran, compared with Qatar, Kuwait and Oman, is mainly because of full coverage of vaccination against hepatitis B in our country.²

In summary, the GBD 2010 digestive diseases ranking (by YLDs) or even the YLLs rankings of the top causes (e.g., cirrhosis) within this disease group do not actually represent our country profile and even is despite the results released from national studies mentioned.⁵⁻⁶ On the other hand, the downward rank of GI diseases reported in GBD 2010 may mask the significance of this group of diseases from the perspective of health policy-makers. However, the inconsistent figures emerging from GBD 2010 indicate how important it will be to conduct periodic national burden of disease studies using all local sources.

Compared with the previous national study, the notable advantages of the current study are as follows. First, we will analyze the trends of the epidemiological data for the selected GI diseases in both national and provincial levels. Second, the study team will generate disease list corresponding to the national disease profile. Third, for many diseases, such as peptic ulcer and IBD the scope of information does not include data from other sources and also there is only a small fraction of data in our published literature. Therefore, we will utilize all existing sources to gather primary data along with routinely collected data. Fourth, although there is a scatter of GI endoscopic data across different health insurance agencies in Iran, this source of data is not sufficiently comprehensive to process all endoscopic data and generate needed reports. For this reason, our study will plan to establish a national and structured endoscopic database to capture indications and costs for endoscopic procedures throughout the country. Fifth, a key challenge for the current study will be the quantification of uncertainty in the resulting estimates. Despite the importance of uncertainty in epidemiological estimates, a recent systematic review of 31 studies on burden of disease showed that none of the studies had quantified uncertainty.²⁴ Uncertainty in the current study will arise from different sources such as statistical models, sampling error, systematic errors in primary data, heterogeneity due to differences in the nature of data sources, variation of national registration systems across provinces. Fifth, although the 86 % cover-

age for Iran death registry is reasonably well,²³ the problem of misclassification already exists, thus we will assess the accuracy of the cause of death reported on the death certificates. Finally, we will deal with incomplete coverage for GI cancers, using the estimates of cancer registry coverage to figure out the actual number of cancer cases in Iran.

Despite our extensive effort for data collection, we will definitely face lack of data in certain GI disorders such as cirrhosis. To address this limitation we will use appropriate mathematical models for cross-walking from actual quantities to the estimated values.²⁹

In conclusion, this study is the first systematic attempt to fill the existing important gaps in knowledge on the epidemiology of main gastrointestinal diseases in Iran. Results of the present study will have implications for policy making, as they allow for understanding geographic distributions of the selected GI diseases, and identifying health disparities across provinces.

Author's Contribution

General designing of the paper was by the NASBOD core team. Shifteh Abedian, Seyed Mohammad Kalantar Motamedi, Mohammad Masoud Malekzadeh, Hamid Mohaghegh, Anahita Sadeghi and Sadaf G. Sepanlou have had equal contribution and the order of their names is alphabetical. All co-authors had contribution in designing of systematic review, primary draft, preparation and revision. All authors have given approval to the final version of the manuscript.

Acknowledgments

The study is granted by Ministry of Health and Medical Education of Islamic Republic of Iran; Setad-e-jeiraie farmane Imam.

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Table1. Clinical and Practical Definitions of Selected Gastrointestinal and Liver Diseases

	Disease	Clinical definition	Practical definition	ICD-10 Cods
1	Peptic ulcer disease	A deep mucosal break with abdominal pain, dyspepsia, and /or bleeding or perforation due to H pylori infection and NSAIDs	Report of peptic ulcer in endoscopic report	K25–K28
2	Cirrhosis of the liver	Any person with chronic liver disease presenting with ascites, and/or variceal bleeding and/or hepatic encephalopathy and/or low platelet with shrinked liver and enlarged spleen in imaging evaluations	Clinico-pathological and/or radiological finding of shrinked liver with ascites, hepatic encephalopathy, or variceal bleeding	K70–K76
3	Appendicitis	Acute right lower quadrant abdominal pain, and inflamed appendix in surgery	Appendectomy reports	K35–K38
4	Hepatitis B	A DNA viral illness which primarily affects the liver, causing acute, and chronic liver disease and is the most common cause of liver cancer	Every person with positive HBs Ag	B16, B17.0, B18.0, B18.1
5	Hepatitis C	An RNA virus which primarily affects the liver and cause chronic liver disease, and liver cell cancer	Every person with positive anti-HCV	B17.1, B18.2
6	Inflammatory bowel disease due to ulcerative colitis & Crohn's disease	Any person with abdominal discomfort/pain, and/or chronic diarrhea with or without bleeding and inflamed/ ulcerated colon mucosa in endoscopy or surgical pathology	Any patient with chronic diarrhea or abdominal pain, with colitis or enteritis in endoscopic finding and/or who has put on 5 ASA and/or immunomodulator therapy	K50, K51
7	Vascular disorders of intestine	Any acute abdominal pain with ischemia or necrosis of the large or small intestine	Any acute abdomen with bowel ischemia or gangrene and/or resection	K55
8	Gallstone & complications	Presence of gallstone in ultrasonography, or other radiological studies	The rate of cholecystectomies according to hospital data/ or mortality data	K80
9	GERD/Dyspepsia	Epigastric discomfort, pain, burning, fullness or early satiety, and /or sub sternal burning for more than 6 weeks	Upper abdominal pain and or discomfort and/ or burning sensation	K20, K21, K22.1, K22.2
10	Constipation	Bowel movements less than three times per week, or passage of hard stools, associated with difficult defecation	ROME II or III criteria	K59.0
11	Celiac disease	A small bowel mucosal disease which is due to sensitivity to gluten part of wheat, rye or barely	Positive celiac serology associated with small intestinal mucosal atrophy	K90.0
12	Irritable bowel syndrome	A chronic lower/diffuse abdominal pain with change in bowel habits with no pathological finding in GI tract	According to ROME II or III criteria	K58
13	Fatty liver	Detection of fat in liver by radiological or pathological methods in the absence of alcohol ingestion	Report of fatty liver in sonography with or without abnormal liver function test	K76.0
14	Hemorrhoid	Dilated prominent veins in the rectum and anus with bleeding or pain	Painless non-significant fresh rectal bleeding or painful thrombosis	K64
15	Anal fissure	A small break in the skin portion of anal canal with bleeding and painful defecation	Painful non-significant fresh rectal bleeding	K60
16	Upper GI bleeding	Vomiting of blood or coffee ground with or without tarry stool or positive occult blood in stool	Any case of hematemesis and/or melena presenting acutely and admits in hospital	K29
17	Stomach cancer	Malignant proliferation of gastric mucosal lining	Pathologic report of gastric adenocarcinoma	C16.1–C16.9
18	Esophagus cancer	Malignant proliferation of esophageal mucosal lining	Pathologic report of esophageal squamous cell carcinoma or adenocarcinoma	C15.0–C15.9
19	Colon and rectum cancers	Malignant proliferation of colorectal mucosal lining	Pathologic report of colorectal adenocarcinoma	C18.0–C20.9
20	Primary liver cancer (Hepatocellular carcinoma)	Malignant primary Liver mass	Liver mass, with typical radiological appearance, and/or high alpha fetoprotein and /or positive biopsy finding	C22.0–C22.9
21	Pancreas cancer	Malignant primary pancreatic mass	Ejection of pancreas mass in imaging studies, and/or positive biopsy finding	C25.0–C25.9

Appendix A: Search strategy and search terms

Mesh Terms	Appendicitis , Appendectomy
Entry Terms	Ruptured Appendicitis , Perforated Appendicitis, Appendectomies
Emtree	appendicitis
PubMed Search terms	((("Iran"[Mesh] OR Iranian OR Iranians OR I.R.Iran)) AND ((("Appendicitis"[Mesh] OR "Ruptured Appendicitis" OR "Perforated Appendicitis") OR "Appendectomy"[Mesh] OR "Appendectomies"))
ISI, Scopus Search Terms	((("Iran" OR "Iranian" OR "Iranians" OR "I.R.Iran") AND ((("Appendicitis" OR "Ruptured Appendicitis" OR "Perforated Appendicitis") OR "Appendectomy" OR "Appendectomies"))

Table 2. Upper GI Bleeding

Mesh Terms	Gastrointestinal Hemorrhage, Esophageal and Gastric Varices , Angiodysplasia, Duodenal Ulcer
Entry Terms	Gastrointestinal Hemorrhages, Gastric Varix ,Gastric Varices, Esophageal Avarices, Esophageal ulcers , Angiodysplasias , Duodenal Ulcers, Curling Ulcer
Emtree	upper gastrointestinal bleeding, upper digestive hemorrhage, upper digestive tract hemorrhage, upper gastrointestinal hemorrhage, upper gastrointestinal tract bleeding
PubMed Search terms	((("Gastrointestinal Hemorrhage"[Mesh] OR "Gastrointestinal Hemorrhages" OR "Esophageal and Gastric Varices"[Mesh] OR "Gastric Varix" OR "Gastric Varices" OR "Esophageal Varices" OR "Esophageal Varix") OR "Angiodysplasia"[Mesh] OR "Angiodysplasias") OR "Duodenal Ulcer"[Mesh] OR "Duodenal Ulcers" OR "Curling Ulcer")) AND ("Iran"[Mesh] OR Iranian OR Iranians OR I.R.Iran)
ISI, Scopus Search Terms	("Gastrointestinal Hemorrhage" OR "Gastrointestinal Hemorrhages" OR "upper gastrointestinal bleeding" OR "upper digestive hemorrhage" OR "upper digestive tract hemorrhage" OR " upper gastrointestinal hemorrhage" OR "upper gastrointestinal tract bleeding" OR "Esophageal and Gastric Varices" OR "Gastric Varix" OR "Gastric Varices" OR "Esophageal Varices" OR "Esophageal Varix" OR "Angiodysplasia" OR "Angiodysplasias" OR "Duodenal Ulcer" OR "Duodenal Ulcers" OR "Curling Ulcer") AND ("Iran"[Mesh] OR Iranian OR Iranians OR I.R.Iran)

Table 3. Celiac disease

Mesh Terms	Celiac Disease
Entry Terms	Gluten Enteropathy, Gluten Enteropathies ,Gluten-Sensitive Enteropathy , Gluten Sensitive Enteropathy ,Gluten-Sensitive Enteropathies ,Nontropical Sprue ,Celiac Sprue
Emtree	celiac disease adult celiac disease celiac sprue celiac syndrome coeliac disease coeliaky gluten Enteropathy gluten induced Enteropathy gluten intolerance gluten sensitive enteropathy nontropical sprue
PubMed Search terms	((("Iran"[Mesh] OR "Iranian" OR "Iranians" OR "I.R.Iran")) AND ("Celiac Disease"[Mesh] OR "Gluten Enteropathy" OR "Gluten Enteropathies" OR "Gluten-Sensitive Enteropathy" OR "Gluten Sensitive Enteropathy" OR "Gluten-Sensitive Enteropathies" OR "Nontropical Sprue" OR "Celiac Sprue"))
ISI, Scopus Search Terms	((("Iran"[Mesh] OR "Iranian" OR "Iranians" OR "I.R.Iran")) AND ("Celiac Disease"[Mesh] OR "Gluten Enteropathy" OR "Gluten Enteropathies" OR "Gluten-Sensitive Enteropathy" OR "Gluten Sensitive Enteropathy" OR "Gluten-Sensitive Enteropathies" OR "Nontropical Sprue" OR "Celiac Sprue" OR "adult celiac disease" OR "celiac syndrome" OR "coeliac disease" OR "coeliaky" OR "gluten induced Enteropathy" OR "gluten intolerance")

Table 4. IBS

Mesh Terms	IRRITABLE BOWEL SYNDROME
Entry Terms	Irritable Bowel Syndromes, Irritable Colon, Mucous Colitides ,Mucous Colitis
Emtree	irritable colon , colon spasm, colonospasm irritable bowel syndrome, irritable colon syndrome mucomembraneous colitis, mucomembranous colitis mucous colitis, spastic colitis spastic colon, unstable colon
PubMed Search terms	((("Irritable Bowel Syndrome"[Mesh] OR "Irritable Bowel Syndromes" OR "Irritable Colon" OR "Mucous Colitides" OR "Mucous Colitis")) AND ((("Iran"[Mesh] OR "Iranian" OR "Iranians" OR "I.R.Iran"))
ISI, Scopus Search Terms	("Irritable Bowel Syndrome" OR "Irritable Bowel Syndromes" OR "Irritable Colon" OR "Mucous Colitides" OR "Mucous Colitis" OR "colon spasm" OR "colonospasm" OR "mucomembraneous colitis" OR "mucomembranous colitis" OR "spastic colitis" OR "spastic colon" OR "unstable colon") AND ("Iran"[Mesh] OR "Iranian" OR "Iranians" OR "I.R.Iran")

Table 5. GALLSTONE & COMPLICATIONS

Mesh Terms	Gallstones , Cholelithiasis, “Cholecystitis, Acute”, Jaundice, “Jaundice, Obstructive”, Pancreatitis
Previous Mesh	Cholelithiasis (1965–2003) Common Bile Duct Calculi (1965–2003)
Entry Terms	Gall Stones ,Biliary Calculi, Gall Stone ,Common Bile Duct Calculi ,Common Bile Duct Gallstones ,Common Bile Duct Gall Stones ,Cholelithiasis, Cholelithiasis , Acute Cholecystitis , Hemolytic Jaundices , Hemolytic Jaundices, Icterus , Obstructive Jaundice, Mechanical Jaundice, Cholestatic Jaundice
Emtree	<p>gallstone bile stone gall stone gallstones intrahepatic gallstone cholelithiasis bile lithiasis bile lithogenicity biliary calculi biliary lithiasis biliary tract calculus cholecystolithiasis cholethiasis gall bladder stone gallbladder calculus gallbladder stone gallstone disease Cholecystitis Cholangiocholecystitis gall bladder infection gallbladder infection gallbladder inflammation obstructive jaundice cholestatic icterus cholestatic jaundice mechanical icterus mechanical jaundice obstructive icterus retention icterus retention jaundice pancreas inflammation pancreatic inflammation</p>
PubMed Search terms	<p>(((((“Gallstones”[Mesh] OR “Gall Stones” OR “Biliary Calculi” OR “Gall Stone” OR “Common Bile Duct Calculi” OR “Common Bile Duct Gallstones” OR “Common Bile Duct Gall Stones”) OR “Cholelithiasis”[Mesh] OR “Cholelithiasis”) OR “Cholecystitis, Acute”[Mesh] OR “Acute Cholecystitis”) OR (“Jaundice”[Mesh] OR “Jaundice, Obstructive”[Mesh]) OR “Hemolytic Jaundices” OR “Icterus” OR “Obstructive Jaundice” OR “Mechanical Jaundice” OR “Cholestatic Jaundice”) OR “”[Mesh] OR “Pancreatitides”)) AND (“Iran”[Mesh] OR “Iranian” OR “Iranians” OR “I.R.Iran”))</p>
ISI, Scopus Search Terms	<p>(“Gallstones” OR “Gall Stones” OR “Biliary Calculi” OR “Gall Stone” OR “bile stone” OR “Common Bile Duct Calculi” OR “Common Bile Duct Gallstones” OR “Common Bile Duct Gall Stones” OR “Cholelithiasis” OR “Cholelithiasis” OR “Acute Cholecystitis” OR “Hemolytic Jaundices” OR “Icterus” OR “Obstructive Jaundice” OR “Mechanical Jaundice” OR “Cholestatic Jaundice” OR “Pancreatitides” OR “intrahepatic gallstone” OR “Bile lithiasis” OR “bile lithogenicity” OR “biliary calculi” OR “biliary lithiasis” OR “biliary lithiasis” OR “biliary tract calculus” OR “gall bladder stone” OR “gallbladder calculus” OR “gallbladder stone” OR “gallstone disease” OR “Cholangiocholecystitis” OR “gall bladder infection” OR “gallbladder infection” OR “gallbladder inflammation” OR “cholestatic icterus” OR “mechanical icterus” OR “obstructive icterus” OR “retention icterus” OR “retention jaundice” OR “pancreas inflammation” OR “pancreatic inflammation”) AND (“Iran”[Mesh] OR “Iranian” OR “Iranians” OR “I.R.Iran”))</p>

Table 6. Dyspepsia, GERD

Mesh Terms	Dyspepsia Gastroesophageal Reflux Heartburn
Entry Terms	Dyspepsias, Indigestion, Indigestions, Gastric Acid Reflux, Gastric Acid Reflux Disease, Gastro-Esophageal Reflux, Gastro Esophageal Reflux, Gastroesophageal Reflux Disease, GERD, Esophageal Reflux, Gastro-oesophageal Reflux, Gastro oesophageal Reflux, Pyrosis, Pyroses
Emtree	dyspepsia dyspepsy dyspeptic disorder dyspeptic syndrome functional dyspepsia postprandial dyspepsia heartburn heart burn pyrosis gastroesophageal reflux cardioesophageal reflux esophageal reflux esophageal regurgitation esophagogastric reflux esophagus reflux gastric regurgitation gastro esophageal reflux gastroesophageal reflex gastroesophageal reflux disease gastroesophageal regurgitation gastroesophagus reflux gastroesophageal reflux disease GERD (gastroesophageal reflux disease) GORD (gastroesophageal reflux disease) oesophageal reflux oesophagus reflux
PubMed Search terms	((("Dyspepsia"[Mesh] OR "Dyspepsias" OR "Indigestion" OR "IndigestionS") OR "Gastroesophageal Reflux"[Mesh] OR "Gastric Acid Reflux" OR "Gastric Acid Reflux Disease" OR "Gastro-Esophageal Reflux" OR "Gastro Esophageal Reflux" OR "Gastroesophageal Reflux Disease" OR "GERD" OR "Esophageal Reflux" OR "Gastro-oesophageal Reflux" OR "Gastro oesophageal Reflux" OR "Heartburn"[Mesh] OR "Pyrosis" OR "Pyroses")) AND (("Iran"[Mesh] OR "Iranian" OR "Iranians" OR "I.R.Iran"))
ISI, Scopus Search Terms	("Dyspepsia" OR "Dyspepsias" OR "Indigestion" OR "IndigestionS" OR "Gastroesophageal Reflux" OR "Gastric Acid Reflux" OR "Gastric Acid Reflux Disease" OR "Gastro-Esophageal Reflux" OR "Gastro Esophageal Reflux" OR "Gastroesophageal Reflux Disease" OR "GERD" OR "Esophageal Reflux" OR "Gastro-oesophageal Reflux" OR "Gastro oesophageal Reflux" OR "Heartburn" OR "Pyrosis" OR "Pyroses" OR "dyspepsy" OR "dyspeptic disorder" OR "dyspeptic syndrome" OR "functional dyspepsia" OR "postprandial dyspepsia" OR "heart burn" OR "cardioesophageal reflux" OR "esophageal regurgitation" OR "esophagogastric reflux" OR "esophagus reflux" OR "gastric regurgitation" OR "gastroesophageal regurgitation" OR "gastroesophagus reflux" OR "gastroesophageal reflux disease" OR "GORD (gastroesophageal reflux disease)" OR "Oesophageal reflux" OR "oesophagus reflux") AND (("Iran"[Mesh] OR "Iranian" OR "Iranians" OR "I.R.Iran"))

Table 7. Peptic Ulcer

Mesh Terms	Peptic Ulcer, Peptic Ulcer Perforation Peptic Ulcer Hemorrhage Duodenal Ulcer Stomach Ulcer
Entry Terms	Peptic Ulcers ,Gastroduodenal Ulcer, Gastroduodenal Ulcers, Marginal Ulcer, Marginal Ulcers, Peptic Ulcer Hemorrhages, Peptic Ulcer Perforations Duodenal Ulcers, Curling Ulcer ,Curling's Ulcer, Curlings Ulcer OR "Stomach Ulcers, Gastric Ulcer Gastric Ulcers
Emtree	peptic ulcer acid peptic disease acute peptic ulcer chronic peptic ulcer gastro duodenal ulcus gastroduodenal ulcer peptic ulcer disease peptic ulceration peptic ulcus ulcus gastro duodenalis ulcus pepticum stomach ulcer acute gastric ulcer gastric peptic ulcer gastric ulcer gastric ulceration gastric ulcus peptic stomach ulcer stomach bleeding ulcer stomach peptic ulcer stomach ulceration stomach ulcus stomach ulcus callosum ulcus callosum ulcus ventriculi ventricular ulcer duodenum ulcer curling's ulcer curling ulcer duodenal peptic ulcer duodenal ulcer duodenal ulceration duodenum bulb ulcer duodenum chronic ulcer duodenum peptic ulcer duodenum recurrent ulcer duodenum ulceration duodenum ulcus stress ulcer,curling ulcus duodeni ulcus duodeni pepticum ulcus pepticum duodeni
PubMed Search terms	((("Peptic Ulcer"[Mesh] OR "Peptic Ulcer Perforation"[Mesh] OR "Peptic Ulcer Hemorrhage"[Mesh] OR "Peptic Ulcers" OR "Gastroduodenal Ulcer" OR "Gastroduodenal Ulcers" OR "Marginal Ulcer" OR "Marginal Ulcers" OR "Peptic Ulcer Hemorrhages" OR "Peptic Ulcer Perforations") OR "Duodenal Ulcer"[Mesh] OR "Duodenal Ulcers" OR "Curling Ulcer" OR "Curling's Ulcer" OR "Curlings Ulcer") OR "Stomach Ulcer"[Mesh] OR "Stomach Ulcers" OR "Gastric Ulcer" OR "Gastric Ulcers")) AND (("Iran"[Mesh] OR "Iranian" OR "Iranians" OR "I.R.Iran"))
ISI, Scopus Search Terms	("Peptic Ulcer" OR "Peptic Ulcer Perforation" OR "Peptic Ulcer Hemorrhage" OR "Peptic Ulcers" OR "Gastroduodenal Ulcer" OR "Gastroduodenal Ulcers" OR "Marginal Ulcer" OR "Marginal Ulcers" OR "Peptic Ulcer Hemorrhages" OR "Peptic Ulcer Perforations" OR "Duodenal Ulcer" OR "Duodenal Ulcers" OR "Curling Ulcer" OR "Curling's Ulcer" OR "Curlings Ulcer" OR "Stomach Ulcer" OR "Stomach Ulcers" OR "Gastric Ulcer" OR "Gastric Ulcers" OR "acid peptic disease" OR "acute peptic ulcer" OR "chronic peptic ulcer" OR "gastro duodenal ulcus" OR "gastroduodenal ulcer" OR "peptic ulcer disease" OR "peptic ulceration" OR "peptic ulcus" OR "ulcus gastro duodenalis" OR "ulcus pepticum" OR "acute gastric ulcer" OR "gastric peptic ulcer" OR "gastric ulceration" OR "gastric ulcus" OR "peptic stomach ulcer" OR "stomach bleeding ulcer" OR "stomach peptic ulcer" OR "stomach ulceration" OR "stomach ulcus" OR "stomach ulcus callosum" OR "ulcus callosum" OR "ulcus ventriculi" OR "ventricular ulcer" OR "duodenal peptic ulcer" OR "duodenal ulceration" OR "duodenum bulb ulcer" OR "duodenum chronic ulcer" OR "duodenum peptic ulcer" OR "duodenum recurrent ulcer" OR "duodenum ulceration" OR "duodenum ulcus" OR "ulcus duodeni") AND ("Iran"[Mesh] OR "Iranian" OR "Iranians" OR "I.R.Iran"))

Table 8. Fatty Liver

Mesh Terms	“Fatty liver”, Fatty Liver, Alcoholic”, Non-alcoholic Fatty Liver Disease”
Entry Terms	Steatohepatitis Steatohepatitides Visceral Steatosis Steatosis of Liver Liver Steatosis Liver Steatoses Alcoholic Fatty Liver Alcoholic Steatohepatitis NAFLD Nonalcoholic Fatty Liver Disease
Emtree	fatty liver fat liver fatty liver infiltration fatty liver syndrome hepatic steatosis hepatosteatoses liver fatty infiltration liver steatosis
PubMed Search terms	((“Fatty Liver”[Mesh] OR “Fatty Liver, Alcoholic”[Mesh] OR “Non-alcoholic Fatty Liver Disease”[Supplementary Concept] OR “Acute fatty liver of pregnancy”[Supplementary Concept] OR “Steatohepatitis” OR “Steatohepatitides” OR “Visceral Steatosis” OR “Steatosis of Liver” OR “Liver Steatosis” OR “Liver Steatoses” OR “Alcoholic Fatty Liver” OR “Alcoholic Steatohepatitis” OR “NAFLD” OR “Nonalcoholic Fatty Liver Disease”)) AND ((“Iran”[Mesh] OR “Iranian” OR “Iranians” OR “I.R.Iran”))
ISI, Scopus Search Terms	(“Fatty Liver” OR “Fatty Liver, Alcoholic” OR “Non-alcoholic Fatty Liver Disease” OR “Acute fatty liver of pregnancy” OR “Steatohepatitis” OR “Steatohepatitides” OR “Visceral Steatosis” OR “Steatosis of Liver” OR “Liver Steatosis” OR “Liver Steatoses” OR “Alcoholic Fatty Liver” OR “Alcoholic Steatohepatitis” OR “NAFLD” OR “Nonalcoholic Fatty Liver Disease” OR “fat liver” OR “fatty liver infiltration” OR “fatty liver syndrome” OR “hepatic steatosis” OR “hepatosteatoses” OR “liver fatty infiltration” OR “liver steatosis”) AND ((“Iran”[Mesh] OR “Iranian” OR “Iranians” OR “I.R.Iran”))

Table 9. CONSTIPATION

Mesh Terms	Constipation, Intestinal- pseudo Obstruction
Entry Terms	Dyschezia, Colonic Inertia
Emtree	constipation dyschezia obstipation rectal constipation slow transit constipation
PubMed Search terms	((“Constipation”[Mesh] OR “Dyschezia” OR “Colonic Inertia”)) AND ((“Iran”[Mesh] OR “Iranian” OR “Iranians” OR “I.R.Iran”))
ISI, Scopus Search Terms	(“Constipation” OR “Dyschezia” OR “Colonic Inertia” OR “dyschezia” OR “obstipation” OR “rectal constipation” OR “slow transit constipation”) AND ((“Iran”[Mesh] OR “Iranian” OR “Iranians” OR “I.R.Iran”))

Table 10. Gastric cancer

Mesh Terms	Stomach Neoplasms
Entry Terms	Gastric Cancers, Gastric Cancer, Stomach Cancer, Stomach Cancers, Gastric Neoplasm, Gastric Neoplasms, Cancer of Stomach
Emtree	stomach cancer gastric cancer
PubMed Search terms	((“Iran”[Mesh] OR “Iranian” OR “Iranians OR I.R.Iran”) AND (“Stomach Neoplasms”[Mesh] OR “Gastric Cancers” OR “Gastric Cancer” OR “Stomach Cancer” OR “Stomach Cancers” OR “Gastric Neoplasm” OR “Gastric Neoplasms” OR “Cancer of Stomach”))
ISI, Scopus Search Terms	(“Iran” OR “Iranian” OR “Iranians” OR “I.R.Iran”) AND (“Stomach Neoplasms” OR “Gastric Cancers” OR “Gastric Cancer” OR “Stomach Cancer” OR “Stomach Cancers” OR “Gastric Neoplasm” OR “Gastric Neoplasms” OR “Cancer of Stomach”)

Table 11. Anal Fissure

Mesh Terms	Fissure in Ano
Entry Terms	Anal Fissure, Anal Ulcer, Anal Ulcers
Emtree	anus fissure anal fissura anal fissure anorectal fissure anus fissura fissura ani fissure ani fissure in ano
PubMed Search terms	((("Fissure in Ano"[Mesh] OR "Anal Fissure" OR "Anal Ulcer" OR "Anal Ulcers") AND ((("Iran"[Mesh] OR "Iranian" OR "Iranians" OR "I.R.Iran"))
ISI, Scopus Search Terms	("Fissure in Ano" OR "Anal Fissure" OR "Anal Ulcer" OR "Anal Ulcers" OR "anus fissure" OR "anal fissure" OR "anorectal fissure" OR "anus fissure" OR "fissura ani" OR "fissure ani") AND ((("Iran"[Mesh] OR "Iranian" OR "Iranians" OR "I.R.Iran"))

Table 12. Hemorrhoid

Mesh Terms	Hemorrhoids, Gastrointestinal Hemorrhage, Hemorrhoidectomy, Rectal Prolapse
Entry Terms	Hematochezi, Hematochezias, Hemorrhoidectomies, Rectal Prolapses, Anus Prolapse, Anus Prolapses
Emtree	-
PubMed Search terms	((("Iran"[Mesh] OR "Iranian" OR "Iranians" OR "I.R.Iran")) AND (((("Hemorrhoids"[Mesh] OR "anal bleeding" OR "rectal bleeding") OR "Gastrointestinal Hemorrhage"[Mesh] OR "Hematochezia" OR "Hematochezias") OR "Hemorrhoidectomy"[Mesh] OR "Hemorrhoidectomies") OR "Rectal Prolapse"[Mesh] OR "Rectal Prolapses" OR "Anus Prolapse" OR "Anus Prolapses"))
ISI, Scopus Search Terms	((("Iran" OR "Iranian" OR "Iranians" OR "I.R.Iran") AND ("Hemorrhoids" OR "anal bleeding" OR "rectal bleeding" OR "Gastrointestinal Hemorrhage" OR "Hematochezia" OR "Hematochezias" OR "Hemorrhoidectomy" OR "Hemorrhoidectomies" OR "Rectal Prolapse" OR "Rectal Prolapses" OR "Anus Prolapse" OR "Anus Prolapses"))

Table 13. Vascular disorder of Intestine

Mesh Terms	Mesenteric vascular disease
Entry Terms	--
Emtree	ischemia blood circulation disorder blood flow disorder circulation disorder circulation failure circulatory disorder circulatory disturbance circulatory failure ischaemia
PubMed Search terms	((("Mesenteric vascular disease"[Supplementary Concept] OR "Ischemia" OR "Vascular diseases") OR "Angiodysplasia"[Mesh] OR "Angiodysplasias") OR "Colitis, Ischemic"[Mesh] OR "Ischemic Colitis")) AND ((("Iran"[MeSH]) OR "Iran" OR "IRANIAN" OR "IRANIANS" OR "I.R.IRAN")
ISI, Scopus Search Terms	((("Mesenteric vascular disease"[Supplementary Concept] OR "Ischemia" OR "Vascular diseases") OR "Angiodysplasia"[Mesh] OR "Angiodysplasias") OR "Colitis, Ischemic"[Mesh] OR "Ischemic Colitis" OR "Intestinal blood circulation disorder" OR "Intestinal blood flow disorder" OR "intestinal circulation disorder" OR "intestinal circulation failure" OR "intestinal circulatory disorder" OR "intestinal circulatory disturbance" OR "intestinal circulatory Failure") AND ("Iran"[MeSH]) OR "Iran" OR "IRANIAN" OR "IRANIANS" OR "I.R.IRAN"))

Table 14. Esophageal Cancer

Mesh Terms	Esophageal Neoplasms
Entry Terms	Esophageal Neoplasm, Esophageal Neoplasms, Esophageal Neoplasms ,Esophagus Neoplasms ,Esophagus Neoplasm, Cancer of Esophagus ,Esophageal Cancers, Esophageal Cancer, Cancer of the Esophagus, Esophagus Cancer, Esophagus Cancers
Emtree	esophagus cancer esophageal cancer esophagus neoplasm oesophagus cancer
PubMed Search terms	“Esophageal Neoplasm” OR “Esophageal Neoplasms” OR (“Esophageal Neoplasms”[MeSH]) OR “Esophagus Neoplasms” OR “Esophagus Neoplasm” OR “Cancer of Esophagus” OR “Esophageal Cancers” OR “Esophageal Cancer” OR “Cancer of the Esophagus” OR “Esophagus Cancer” OR “Esophagus Cancers”) AND (“Iran”[MeSH]) OR “Iran” OR “IRANIAN” OR “IRANIANS” OR “I.R.IRAN”)
ISI, Scopus Search Terms	(“Esophageal Neoplasm” OR “Esophageal Neoplasms” OR “Esophagus Neoplasms” OR “Esophagus Neoplasm” OR “Cancer of Esophagus” OR “Esophageal Cancers” OR “Esophageal Cancer” OR “Cancer of the Esophagus” OR “Esophagus Cancer” OR “Esophagus Cancers”) AND (“Iran” OR “Iran” OR “IRANIAN” OR “IRANIANS” OR “I.R.IRAN”)

Table 15. Hepatitis C

Mesh Terms	Hepatitis C; Hepatitis C, Chronic; Hepatitis C Antibodies; Hepacivirus
Entry Terms	Parenterally-Transmitted Non-A, Non-B Hepatitis; Parenterally Transmitted Non A, Non B Hepatitis; PT-NANBH; Hepatitis, Viral, Non-A, Non-B, Parenterally-Transmitted; Chronic Hepatitis C; Hepatitis C Virus Antibodies; HCV Antibodies; Anti-HCV Antibodies; Anti HCV Antibodies; Anti-Hepatitis C Virus Antibodies; Anti Hepatitis C Virus Antibodies; Hepaciviruses; Hepatitis C-Like Viruses; Hepatitis C Like Viruses; Hepatitis C-Like Virus; Hepatitis C virus; Hepatitis C viruses
Emtree	Hepatitis C Non A, Non B Hepatitis
PubMed Search terms	((((Iran*) OR Iranian*) OR I.R.Iran)) AND (((“Hepatitis C”[Mesh]) OR “Hepatitis C, Chronic”[Mesh]) OR “Hepatitis C Antibodies”[Mesh]) OR “Hepacivirus”[Mesh] OR “Parenterally-Transmitted Non-A, Non-B Hepatitis” OR “Parenterally Transmitted Non A, Non B Hepatitis” OR “PT-NANBH” OR “Hepatitis, Viral, Non-A, Non-B, Parenterally-Transmitted” OR “Chronic Hepatitis C” OR “Hepatitis C Virus Antibodies” OR “HCV Antibodies” OR “Anti-HCV Antibodies” OR “Anti HCV Antibodies” OR “Anti-Hepatitis C Virus Antibodies” OR “Anti Hepatitis C Virus Antibodies” OR “Hepaciviruses” OR “Hepatitis C-Like Viruses” OR “Hepatitis C Like Viruses” OR “Hepatitis C-Like Virus” OR “Hepatitis C virus” OR “Hepatitis C viruses”)
ISI, Scopus Search Terms	(Iran* OR Iranian* OR I.R.Iran) AND (“Hepatitis C” OR “Hepatitis C, Chronic” OR “Hepatitis C Antibodies” OR “Hepacivirus” OR “Parenterally-Transmitted Non-A, Non-B Hepatitis” OR “Parenterally Transmitted Non A, Non B Hepatitis” OR “PT-NANBH” OR “Hepatitis, Viral, Non-A, Non-B, Parenterally-Transmitted” OR “Chronic Hepatitis C” OR “Hepatitis C Virus Antibodies” OR “HCV Antibodies” OR “Anti-HCV Antibodies” OR “Anti HCV Antibodies” OR “Anti-Hepatitis C Virus Antibodies” OR “Anti Hepatitis C Virus Antibodies” OR “Hepaciviruses” OR “Hepatitis C-Like Viruses” OR “Hepatitis C Like Viruses” OR “Hepatitis C-Like Virus” OR “Hepatitis C virus” OR “Hepatitis C viruses”)

Table 16. Colon Cancer

Mesh Terms	Colorectal Neoplasms
Entry Terms	“Colorectal Neoplasm” OR “Colorectal Tumors” OR “Colorectal Tumor” OR “Colorectal Carcinoma” OR “Colorectal Carcinomas” OR “Colorectal Cancer” OR “Colorectal Cancers”)
Emtree	--
PubMed Search terms	“Colorectal Neoplasms”[Mesh] OR “Colorectal Neoplasm” OR “Colorectal Tumors” OR “Colorectal Tumor” OR “Colorectal Carcinoma” OR “Colorectal Carcinomas” OR “Colorectal Cancer” OR “Colorectal Cancers”) AND ##“iran”[MeSH Terms] OR “iran”[All Fields]# OR IRANIAN[All Fields] OR IRANIANS[All Fields] OR ##“innervation”[Subheading] OR “innervation”[All Fields] OR “ir”[All Fields]# AND #“iran”[MeSH Terms] OR “iran”[All Fields]### AND #“humans”[MeSH Terms] AND #“1985/01/01”[PDAT] : “2013/01/01”[PDAT]##
ISI, Scopus Search Terms	ISI: Topic=(“Colorectal Neoplasms” OR “Colorectal Neoplasm” OR “Colorectal Tumors” OR “Colorectal Tumor” OR “Colorectal Carcinoma” OR “Colorectal Carcinomas” OR “Colorectal Cancer” OR “Colorectal Cancers”) AND Topic=(“Iran” OR “I.R. Iran” OR “Iranian” OR “Iranians”)

Table 17. Pancrease cancer

Mesh Terms	PANCREATIC NEOPLASMS
Entry Terms	PANCREATIC NEOPLASM, pancreas neoplasms ,pancreas neoplasm, cancer of pancreas, pancreas cancer, pancreas cancers,pancreatic cancer, pancreatic cancers ,cancer of the pancreas
Emtree	Pancreatic neoplasms, Pancreas cancer ,pancreatic cancer
PubMed Search terms	((“PANCREATIC NEOPLASMS”[Mesh] OR “PANCREATIC NEOPLASM” OR “pancreas neoplasms “ OR “pancreas neoplasm” OR “cancer of pancreas” OR “ pancreas cancer” OR “pancreas cancers” OR “pancreatic cancer” OR “pancreatic cancers “ OR “cancer of the pancreas” AND (“Iran”[MeSH]) OR “Iran” OR “IRANIAN” OR “IRANIANS” OR “I.R.IRAN”))
ISI, Scopus Search Terms	((“PANCREATIC NEOPLASMS” OR “PANCREATIC NEOPLASM” OR “pancreas neoplasms “ OR “pancreas neoplasm” OR “cancer of pancreas” OR “ pancreas cancer” OR “pancreas cancers” OR “pancreatic cancer” OR “pancreatic cancers “ OR “cancer of the pancreas”) AND (“Iran” OR “Iran” OR “IRANIAN” OR “IRANIANS” OR “I.R.IRAN”))

Table 18. Inflammatory Bowel Diseases

Mesh Terms	Inflammatory Bowel Diseases
Entry Terms	Inflammatory bowel disease; Bowel Diseases, Inflammatory; Ulcerative Colitis; Crohn’s Disease; Ileocolitis; Ileitis, Terminal; Ileitis, Regional; Colitis, Granulomatous; Enteritis, Granulomatous Enteritis, Regional
Emtree	--
PubMed Search terms	“inflammatory bowel diseases”[MeSH Terms] AND ((“Iran”[MeSH Terms] OR “Iran” [All Fields]) OR Iranian[All Fields] OR Iranians[All Fields] OR I.R.Iran[All Fields])
ISI, Scopus Search Terms	(“Iran” OR “Iranian” OR “Iranians” OR “I.R.Iran”) AND (Inflammatory Bowel Disease OR Bowel Diseases, Inflammatory OR Ulcerative Colitis OR Crohn’s Disease OR Ileocolitis OR Ileitis, Terminal OR Ileitis, Regional OR Colitis, Granulomatous OR Enteritis, Granulomatous OR Enteritis, Regional)

Table 19. Liver cancer

Mesh Terms	Liver Neoplasm
Entry Terms	Neoplasms, Hepatic Neoplasms, Liver Liver Neoplasm Neoplasm, Liver Hepatic Neoplasms Hepatic Neoplasm Neoplasm, Hepatic Cancer of Liver Hepatocellular Cancer Cancers, Hepatocellular Hepatocellular Cancers Hepatic Cancer Cancer, Hepatic Cancers, Hepatic Hepatic Cancers Liver Cancer Cancer, Liver Cancers, Liver Liver Cancers Cancer of the Liver Cancer, Hepatocellular
Emtree	liver cell carcinoma carcinoma, hepatocellular carcinoma,hepatic cell carcinoma,liver carcinoma,liver cell hepatic carcinoma hepatic cell carcinoma hepatocarcinoma hepatocellular carcinoma hepatoma liver carcinoma liver carcinoma rupture malignant hepatoma primary liver carcinoma

PubMed Search terms	("Liver Neoplasms"[Mesh]OR "Neoplasms, Hepatic"OR "Neoplasms, Liver" OR " Liver Neoplasm" OR " Neoplas, Liver" OR" Hepatic Neoplasms" OR " Hepatic Neoplasm" OR" Neoplasm, Hepatic" OR " Cancer of Liver " OR" Hepatocellular Cancer " OR" Cancers, Hepatocellular " OR" Hepatocellular Cancers " OR" Hepatic Cancer " OR" Cancer, Hepatic " OR " Cancers, Hepatic" OR " Hepatic Cancers " OR " Liver Cancer " OR " Cancer, Liver " OR " Cancers, Liver" OR " Liver Cancers " OR " Cancer of the Liver " OR " Cancer, Hepatocellular") AND ("Iran"[MeSH]) OR "Iran" OR "IRANIAN" OR "IRANIANS" OR "I.R.IRAN"))
ISI, Scopus Search Terms	("Liver Neoplasms"OR "Neoplasms, Hepatic"OR "Neoplasms, Liver" OR " Liver Neoplasm" OR " Neoplas, Liver" OR" Hepatic Neoplasms" OR " Hepatic Neoplasm" OR" Neoplasm, Hepatic" OR " Cancer of Liver " OR" Hepatocellular Cancer " OR" Cancers, Hepatocellular " OR" Hepatocellular Cancers " OR" Hepatic Cancer " OR" Cancer, Hepatic " OR "Cancers, Hepatic" OR " Hepatic Cancers " OR " Liver Cancer " OR " Cancer, Liver " OR " Cancers, Liver" OR " Liver Cancers " OR " Cancer of the Liver " OR " Cancer, Hepatocellular") AND ("Iran" OR "Iranian" OR "Iranians" OR "I.R.Iran")

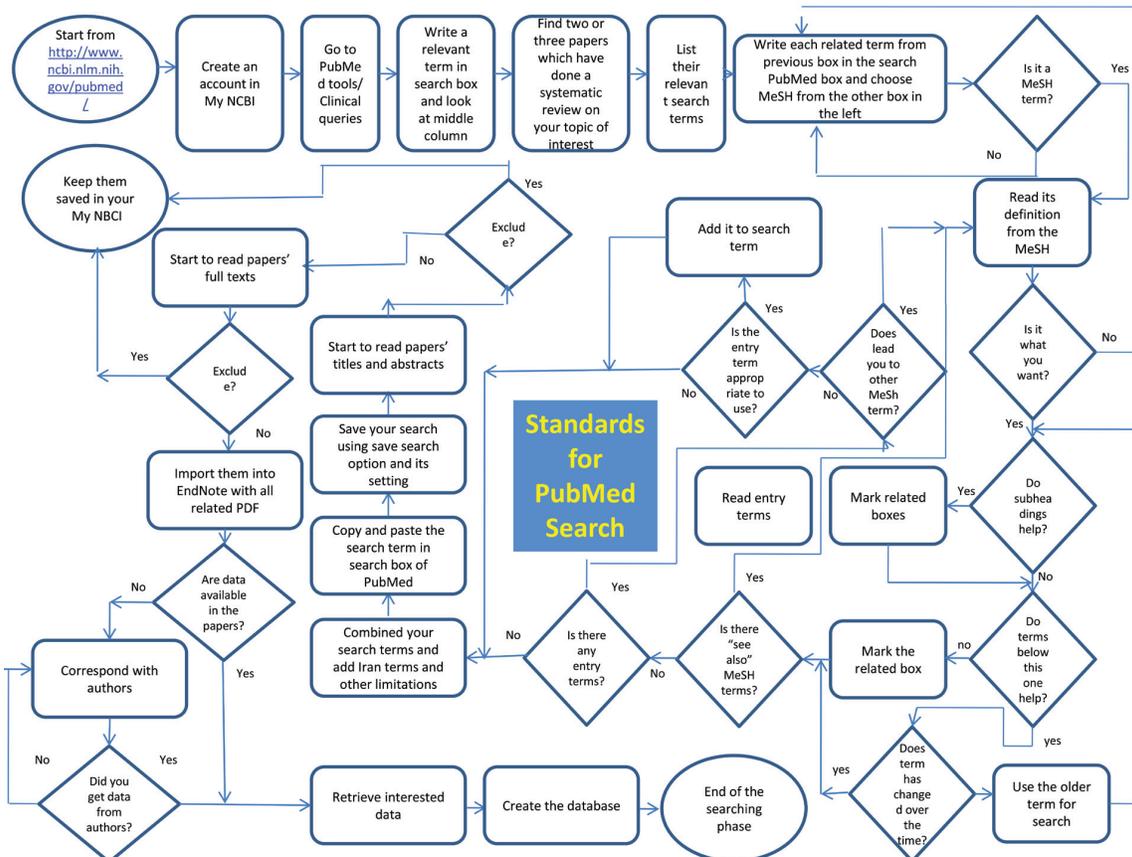
Table 20. Cirrhosis

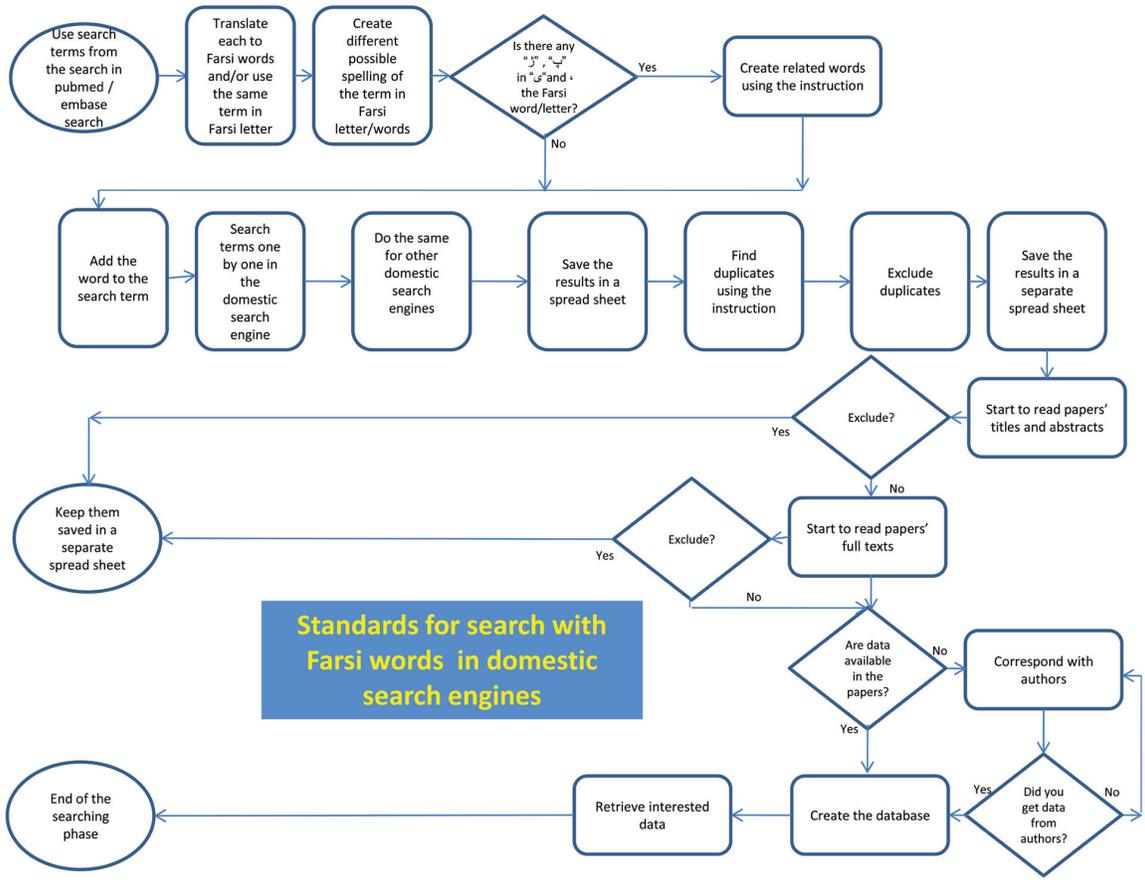
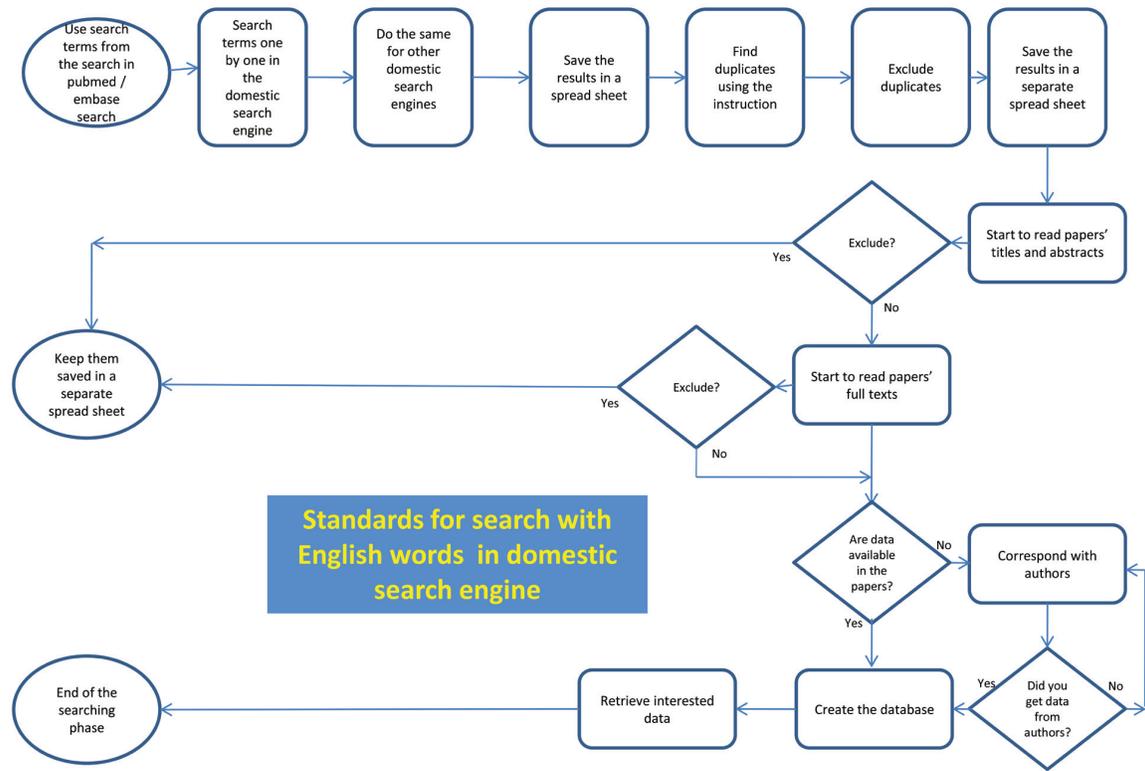
Mesh Terms	Liver Cirrhosis
Entry Terms	Cirrhosis, Liver Cirrhoses, Liver Liver Cirrhoses Hepatic Cirrhosis Cirrhoses, Hepatic Cirrhosis, Hepatic Hepatic Cirrhoses Fibrosis, Liver Fibroses, Liver Liver Fibroses Liver Fibrosis
Emtree	liver cirrhosis cirrhosis cirrhosis hepatitis cirrhosis,liver cryptogenic liver cirrhosis dietary cirrhosis dietary liver cirrhosis hepatic cirrhosis postnecrotic liver cirrhosis liver cirrhosis cirrhosis cirrhosis hepatitis cirrhosis,liver cryptogenic liver cirrhosis dietary cirrhosis dietary liver cirrhosis hepatic cirrhosis postnecrotic liver cirrhosis
PubMed Search terms	("Liver Cirrhosis" [Mesh] OR "Liver Fibrosis" [Mesh] OR "Ascites" [Mesh]OR" Varriceal Hemorrhage" [Mesh] OR" Hepatic Encephalopathy" [Mesh] OR "Cirrhosis, Liver" OR"Cirrhoses, Liver" OR"Liver Cirrhoses" OR"Hepatic Cirrhosis " OR"Fibrosis, Liver " OR"Liver Fibroses " OR"Liver Fibrosis " OR" Fibroses, Liver")AND("Iran"[MeSH] OR "Iran" OR "IRANIAN" OR "IRANIANS" OR "I.R.IRAN")
ISI, Scopus Search Terms	("Liver Cirrhosis" OR "Liver Fibrosis" OR "Ascites" OR" Varriceal Hemorrhage" OR" Hepatic Encephalopathy" OR "Cirrhosis, Liver" OR" Cirrhoses, Liver" OR" Liver Cirrhoses" OR" Hepatic Cirrhosis " OR" Fibrosis, Liver " OR" Liver Fibroses " OR" Liver Fibrosis " OR" Fibroses, Liver")AND("Iran" OR "IRANIAN" OR "IRANIANS" OR "I.R.IRAN")

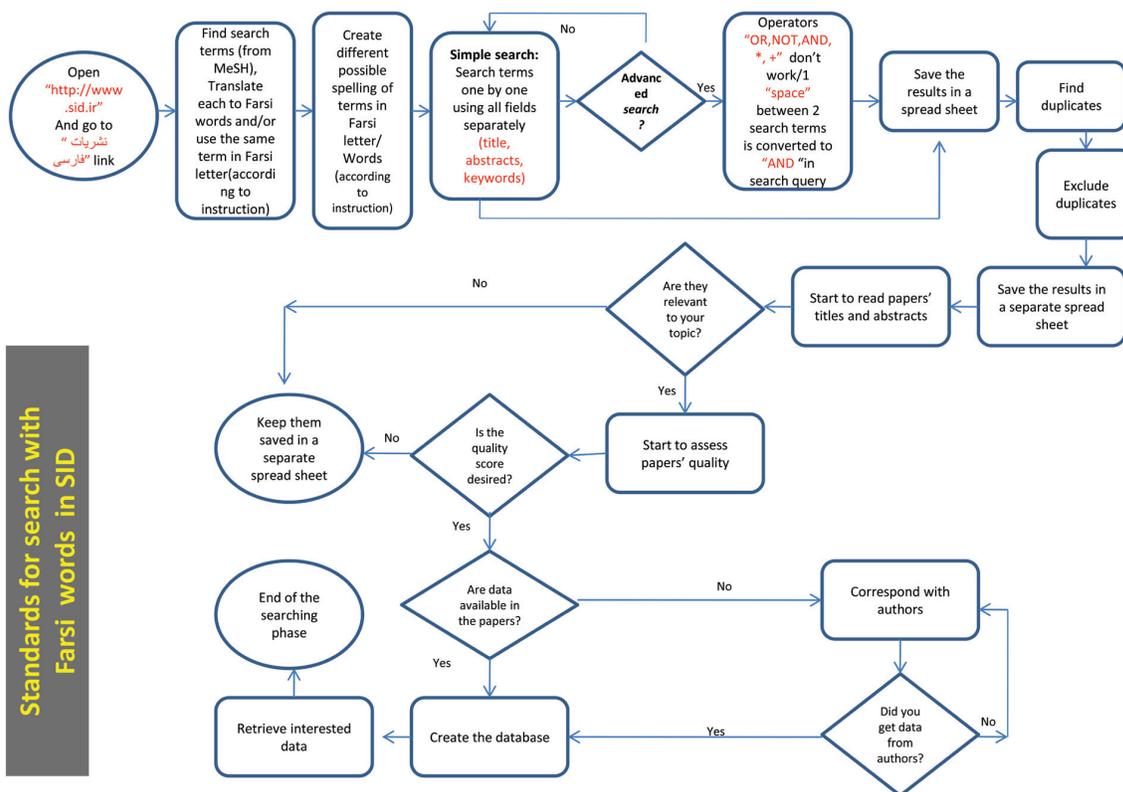
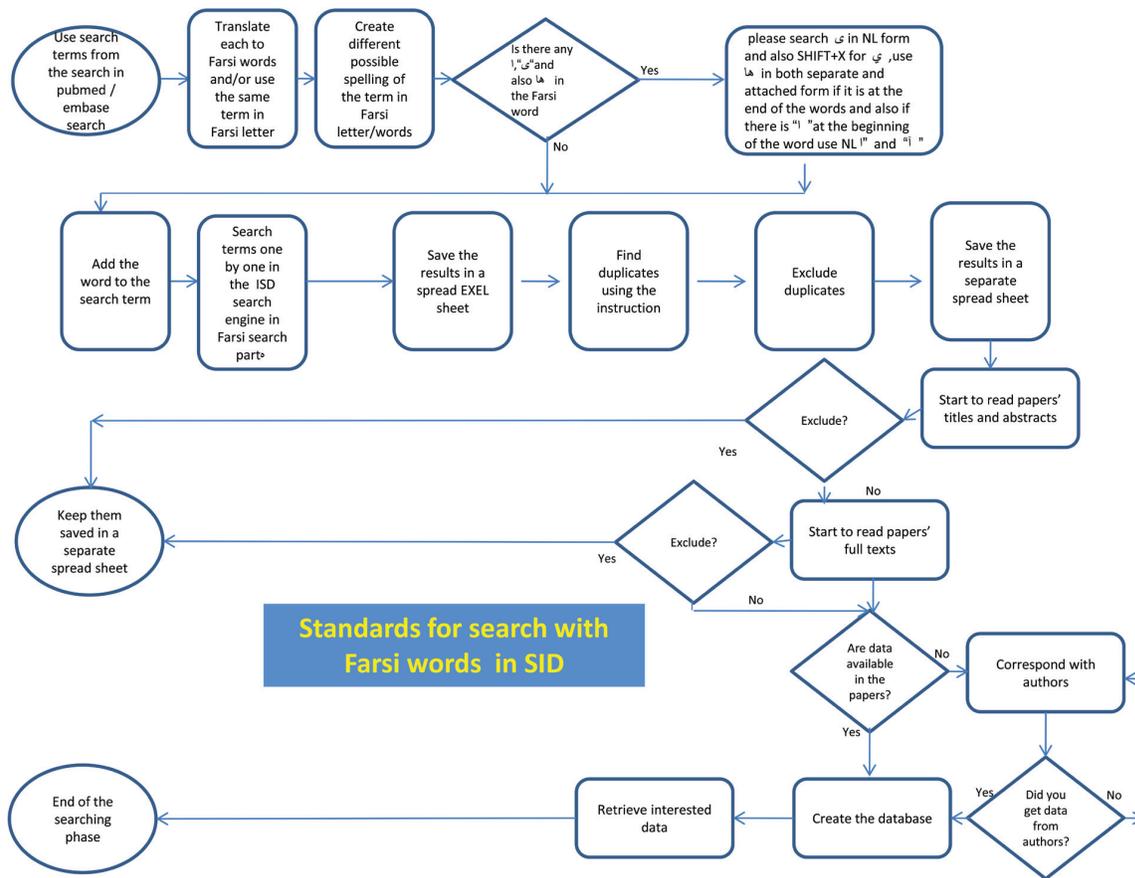
Table 21. Hepatitis B

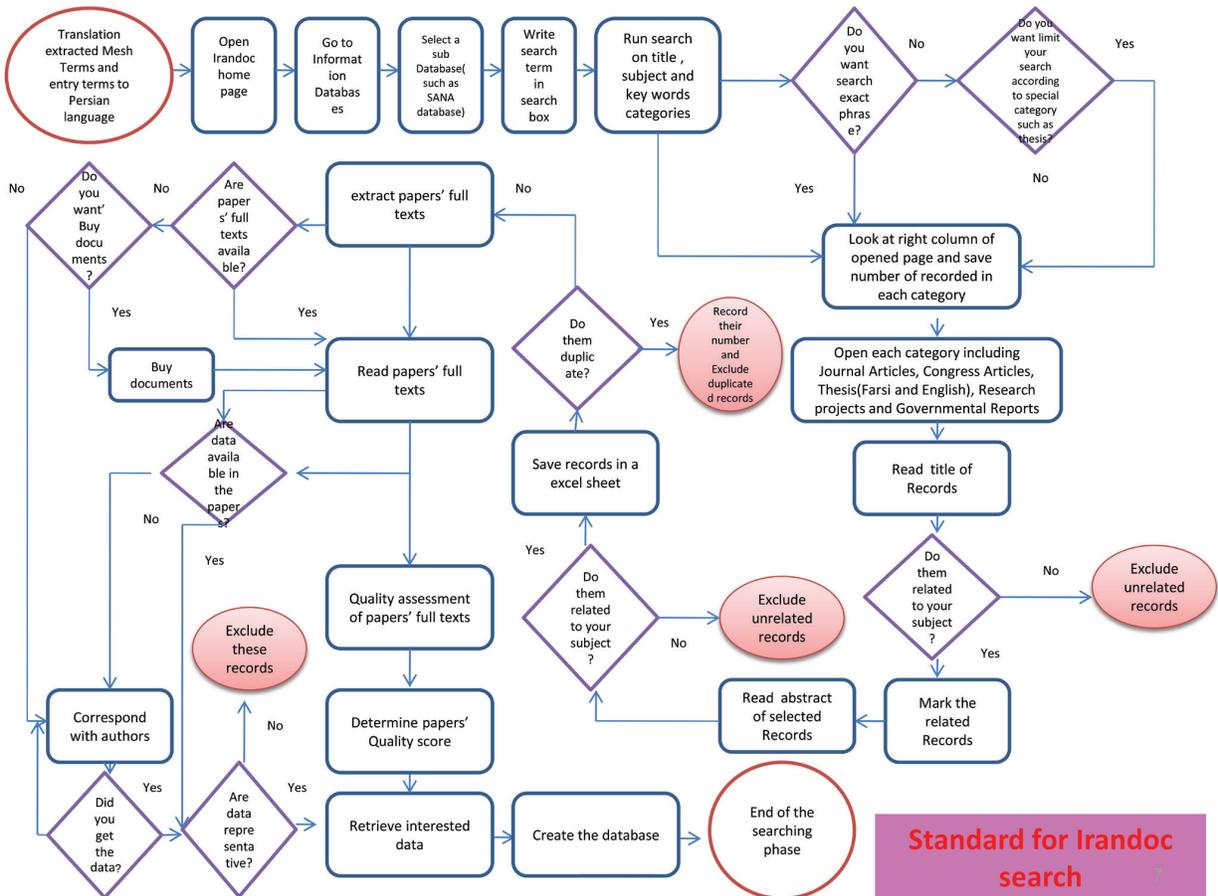
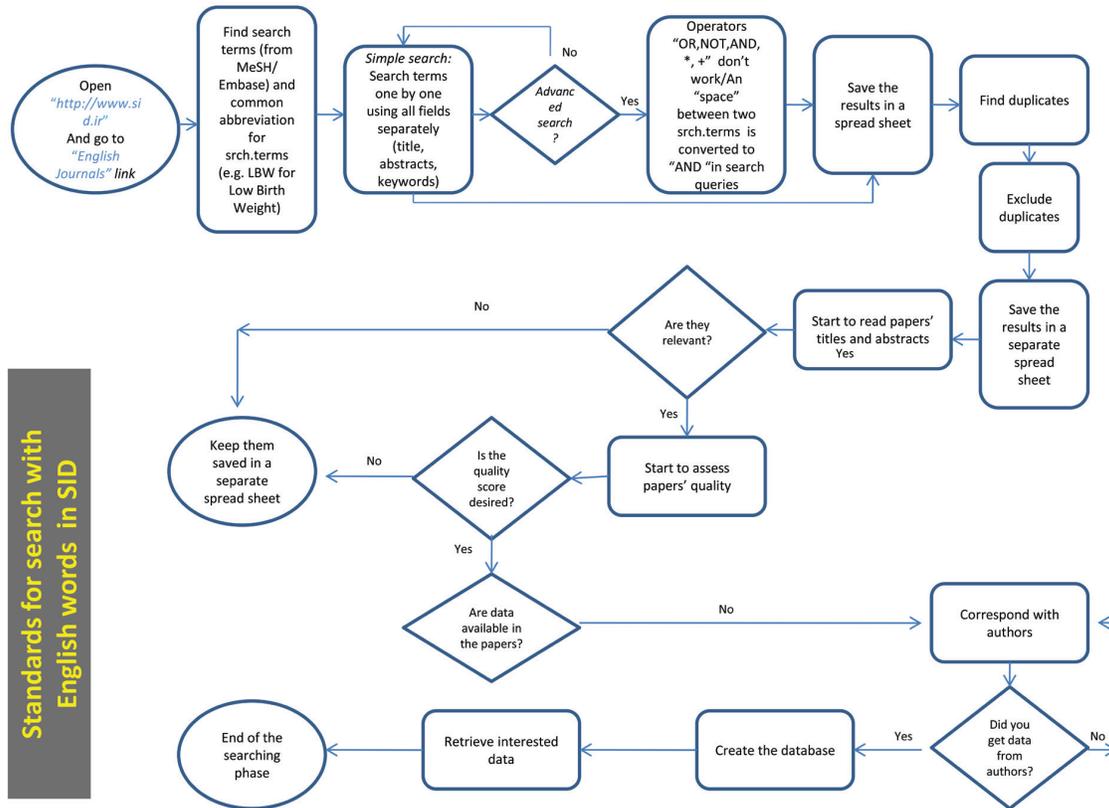
Mesh Terms	Hepatitis B-Hepatitis B, Chronic-Hepatitis B virus-Hepatitis B Surface Antigen-Hepatitis B Antigen-Hepatitis B surface Antigen receptor
Entry Terms	B virus, Hepatitis Hepatitis B viruses virus, Hepatitis B viruses, Hepatitis B Hepatitis B Surface Antigen Australia Antigen Antigen, Australia HBs Ag hepatitis B surface antigen receptors receptor, hepatitis B surface antigen HBs Ag receptor
Emtree	1. hepatitis B 2. hepatitis B, chronic 3. hepatitis, serum 4. hippie hepatitis 5. injection hepatitis 6. serum hepatitis 7. type b hepatitis 8. viral hepatitis type B 9. virus hepatitis type B
PubMed Search terms	("Hepatitis B"[Mesh] OR "Hepatitis B, Chronic"[Mesh] OR "Hepatitis B Antibodies"[Mesh] OR Hepatitis B virus"[Mesh] OR "Hepatitis B Surface Antigens "[Mesh] OR hepatitis B surface antigen receptor "[Mesh] OR " Hepatitis B Vaccine " OR " Hepatitis B viruses" OR " Anti-Hepatitis B Antigens " OR "Chronic Hepatitis B " OR "Hepatitis B Surface Antigen "OR "HBs Ag "OR "hepatitis B surface antigen receptors "OR " HBs Ag receptor ")AND ("Iran" OR "IRANIAN" OR "IRANIANS" OR "I.R.IRAN")
ISI, Scopus Search Terms	("Hepatitis B"OR "Hepatitis B , Chronic" OR "Hepatitis B Antibodies" OR" Hepatitis B virus "OR" Hepatitis B Surface Antigens " OR" hepatitis B surface antigen receptor " OR " Hepatitis B Vaccine " OR " Hepatitis B viruses" OR " Anti-Hepatitis B Antigens " OR "Chronic Hepatitis B " OR "Hepatitis B Surface Antigen "OR "HBs Ag" OR "hepatitis B surface antigen receptors "OR " HBs Ag receptor ")AND ("Iran" OR "IRANIAN" OR "IRANIANS" OR "I.R.IRAN")

Appendix B. Flowcharts









Appendix C. Critical Appraisal Tool

Reviewer <input type="checkbox"/> 1 <input type="checkbox"/> 2	Articles				
	1	2	3	4	5
STEP1. Primary Evaluation Please do this by reading the title/abstract	<input type="checkbox"/> Reject <input type="checkbox"/> Accept				
STEP2. Read the full text deeply and score those articles pass the primary evaluation					
1. Random sample or whole population					
2. Unbiased sampling frame (i.e. census data)					
3. Adequate sample size (> 300 subjects)					
4. Measures were standard					
5. Outcomes measured by unbiased assessors					
6. Adequate response rate (70 %), refuses described					
7. Confidence intervals, subgroup analysis					
Total score					
Final decision	<input type="checkbox"/> Reject <input type="checkbox"/> Accept				
If the article meet the criteria, put score 1 on the cell. Articles with total score more than 5, were entered in the study.					