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Administrative Coding in Electronic Health Care Record-Based Research of NAFLD: An Expert Panel Consensus Statement

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Administrative coding in electronic health care record-based research of NAFLD: an expert panel consensus statement

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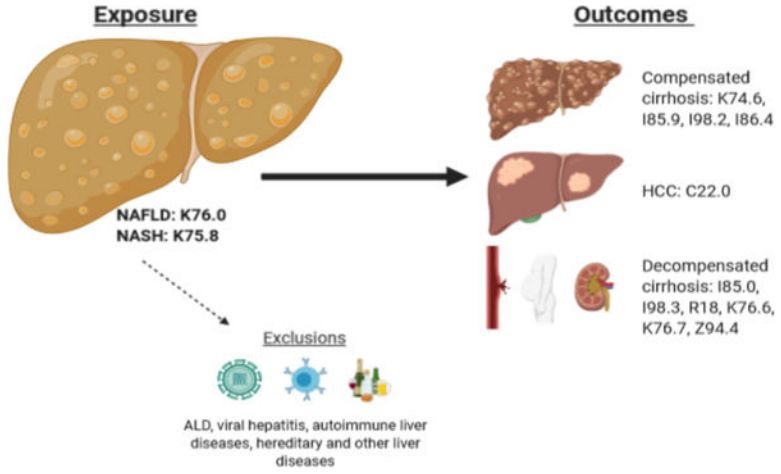
Abstract

Background and aims: Electronic health record (EHR)-based research allows the capture of large amounts of data, which is necessary in nonalcoholic fatty liver disease (NAFLD), where the risk of clinical liver outcomes is generally low. The lack of consensus on which International Classification of Disease (ICD) codes should be used as exposures and outcomes limits comparability and generalizability of results across studies. We aimed to establish consensus among a panel of experts on ICD codes that could become the reference standard and provide guidance around common methodological issues.

Approach and results: Researchers with an interest in EHR-based NAFLD research were invited to collectively define which administrative codes are most appropriate for documenting exposures and outcomes. We used a modified Delphi approach to reach consensus on several commonly encountered methodological challenges in the field. After two rounds of revision, a high level of agreement (>67%) was reached on all items considered. Full consensus was achieved on a comprehensive list of administrative codes to be considered for inclusion and exclusion criteria in defining exposures and outcomes in EHR-based NAFLD research. We also provide suggestions on how to approach commonly encountered methodological issues and identify areas for future research.

Conclusions: This expert panel consensus statement can help harmonize and improve generalizability of EHR-based NAFLD research.

Graphical abstract



Keywords

cirrhosis; epidemiology; health information; hepatocellular carcinoma; MAFLD; NAFLD; registry-based research; steatosis

Introduction

Research using routinely collected data from registries on electronic healthcare records (EHR) is becoming increasingly common with the ongoing digitalization of healthcare and can make valuable contributions to many fields (1). For instance, EHR-based research generally enables the inclusion of a vast number of study participants from multiple sites and, depending on the setting, allows for prospective long-term follow-up or historical cohort data. In nonalcoholic fatty liver disease (NAFLD), there are many examples of EHR-based studies that have provided important insight into the natural history of the disease (2–7) and have helped inform international guidelines (8, 9). This type of research can also be used to identify patients with liver diseases not traditionally seen at hepatology clinics, such as patients with NAFLD seen in primary care or by other hospital-based specialists including endocrinologists and cardiologists (10–14). In addition, population-based health examination studies, which fall under EHR-based research, allow for the identification of persons in the general population who may be unaware of their disease status (15–17). Furthermore, EHR-based studies could be used to assess the safety and real-world effectiveness of new NAFLD drug therapies on patient outcomes outside of clinical trial settings. However, little effort has been made to standardize the definitions of exposures and outcomes in EHR-based NAFLD research, resulting in many different definitions being used by distinct research groups. For instance, no clear guidance exists on how to define the progression of NAFLD to cirrhosis, (i.e. which administrative codes to use), or how to define nonalcoholic steatohepatitis (NASH), and current guidelines do not list suggestions for coding (8, 9). The lack of consensus on definitions threatens the comparability and generalizability of results from different studies. Several methodological considerations, such as how to deal with the risk of misclassification between NAFLD and alcohol-related liver disease (ALD), are also dealt with differently by distinct research

groups. Importantly, few validation studies have been performed to assess the validity of ICD-codes representative of NAFLD/NASH, while codes associated with cirrhosis and hepatocellular carcinoma (HCC) have been validated in different settings (18–23). The aim of this study was to survey researchers, including those engaged in EHR-based research, to understand their views regarding the definitions used to document exposures and outcomes in EHR-based NAFLD research with a focus on liver-related outcomes and to establish a consensus on which codes are most appropriate to use. We chose to focus on diagnostic coding, as many databases do not routinely record data on more detailed parameters such as laboratory data. We have also made some general methodological recommendations for future EHR-based studies in this field.

Materials and methods

A group of researchers with expertise in large-scale database studies in NAFLD field were invited to collaborate. Initial collaborators were then asked to suggest other key researchers to establish a large panel from diverse countries and settings. All invited collaborators that accepted the invitation were asked to supply feedback on an Excel spreadsheet with diagnostic codes relevant to exposures and outcomes in NAFLD research (Table 1). Administrative codes were defined as codes representing the different stages of NAFLD including NASH, fibrosis without cirrhosis, compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma (HCC), liver transplantation, and a list of important specific liver diseases other than NAFLD relevant to the studies in this field. We defined all diagnoses using International Classification of Disease (ICD) coding, versions 8–11. Outdated versions of ICD (version 8 and for some countries version 9) were also included as retrospective studies using historical data might benefit from using such versions, and the upcoming ICD-11 version was used as it is likely to replace older versions in the coming years (available at: https://www.who.int/classifications/icd/en/). Additional information sources such as data on procedure codes and coding for specific pharmacotherapies were also considered.

An online survey, utilizing the platform www.sogosurvey.com, was used to ask methodological questions. After all collaborators had given feedback, answers were collated and anonymized and results were shared using a modified Delphi approach (24). Next, an updated spreadsheet was distributed for additional feedback and the survey was re-distributed giving participants an option to change their replies after feedback from the group. Adding additional questions to the survey could be requested by any collaborator. In the end, the questions were defined as statements that generally could be answered with a “yes” or “no” answer. Consensus was defined as greater than 67% agreement with a statement (25). We highlight statements where consensus was between 67% and 90%, as these might be topics for future studies.

Ethical considerations

No patient-level data were included in this study; thus no ethical approval was required.

Results

A total of 27 collaborators were invited, of which 25 (93%) agreed to collaborate, while one did not reply, and one declined to participate. 90% of participants reported using primarily ICD-10 codes, while the remainder reported using the ICD-9 version. No other coding system was used. The final list of suggested ICD-codes is presented in Table 1. Codes are truncated to the left for diagnoses that include several diagnostic alternatives. For instance, when excluding alcohol-related liver disease in the ICD-10 system, all codes starting with "K70" should be excluded. Therefore, we did not present a more detailed level of codes.

The table lists possible exposure and outcome diagnoses as well as exclusion criteria but does not list an order of how to use these, as the usage of codes should be tailored to specific research questions and data availability across cohorts. All collaborators agreed on the final set of codes.

After two rounds of revision, a >67% consensus was established for all 14 recommendations considered in the final version of the survey, with 6/14 questions having a >90% agreement. The recommendations and the percentage of collaborators that agreed with each statement are listed below. The replies to the first round of the survey are presented in the Appendix (eTable 1). Some questions from the first round of the survey were redundant and some were rephrased or added after suggestions from collaborators.

General recommendations

1. Ideally, specific validation studies should be performed for diagnostic codes across different settings. Preferably, validation studies should obtain random patient charts with the diagnostic code in question, and the gold standard should be defined as a pre-specified set of criteria to calculate positive predictive values (e.g. histological or radiological signs of cirrhosis for code K74.6 [cirrhosis of unspecified origin]). It is particularly important to validate codes representative of NAFLD/NASH. (100% agreement)

2. The order of coding in administrative databases should be actively considered. Many systems use primary and contributing diagnoses. A primary diagnosis usually defines the main event of a hospitalization, with contributing diagnoses that might or might not be associated with that event. Coding for cirrhosis can thus be a primary diagnosis while a contributing diagnosis can be made for the etiologic disease, such as NAFLD. For many research questions, primary codes could be sufficient, but when a more granular level of data is required, it could be more appropriate to use combinations of primary and contributing causes, depending on the research question. For some research questions, only using primary coding could lead to a study unable to consider different causes of cirrhosis. (68% agreement)

3. Where available, the setting of the diagnosis can be used to enhance its validity. For example, a code for cirrhosis might have a higher validity when diagnosed in a hepatology clinic versus a primary care center (18). (67% agreement)

Defining NAFLD/NASH

4. Misclassification of other liver diseases can be common in NAFLD, perhaps most commonly occurring with alcohol-related liver disease (ALD). For studies that examine the risk of "pure" NAFLD, exclusion of concurrent liver diseases should be made using diagnosis codes given before or concurrently with the diagnosis of NAFLD. Suggested codes for these diseases are listed in Table 1. Concurrent liver diseases can also be diagnosed after a diagnosis of NAFLD, but the methodology for how to treat these depends on the research question. (74% agreement)

5. To define NASH, the ICD-10 code K75.8 should be primarily used. However, local / national practices should be considered. (82% agreement)

6. Defining and separating NASH from simple steatosis can be difficult, and in general EHR-based research cannot accurately distinguish NASH from simple steatosis in the absence of biopsy. Studies that try to accomplish a high specificity of correctly identifying NASH could use procedure coding for liver biopsy to increase specificity of the NASH diagnosis (i.e. a code of K75.8 + a code for liver biopsy). In general, this approach should also report the time interval between biopsy and NASH diagnosis to increase transparency. (84% agreement)

Ascertaining progression to cirrhosis

7. When ascertaining progression to cirrhosis, specific coding for cirrhosis needs to be present to define progression to cirrhosis. Studies should not count events, such as hospitalizations, where only coding for NAFLD/NASH is available, as defining cirrhosis. (100% agreement)

8. Liver disease outcomes are generally rare in most populations. A composite outcome, including diagnoses related to complications of cirrhosis of high validity, should generally be applied when ascertaining outcomes associated with cirrhosis. Our recommendations for these are specified in Table 1. For instance, for a person where bleeding esophageal varices are found but there is no diagnosis of cirrhosis or competing cause such as portal vein thrombosis, they should be counted as having cirrhosis. However, the etiology of cirrhosis should be individually determined. Special considerations are also needed for potential liver-related outcomes that could be caused by other underlying conditions (see statement #11). (94% agreement)

Aspects on coding for cirrhosis

9. Specific coding for NAFLD/NASH in patients with cirrhosis might be missing in some registries/databases. Coding for metabolic syndrome components (diabetes type 2, obesity, hypertension, or hyperlipidemia) at or before the cirrhosis event may be considered to improve sensitivity of capturing NAFLD-related cirrhosis outcomes. Such an approach should also be validated in accordance with statement #1. (79% agreement)

10. For hepatocellular carcinoma outcomes, the specific code for HCC should be used (ICD-10: C22.0), as coding for “Liver cancer, unspecified” (ICD-10: C22.9) is likely to have a low specificity for HCC. However, the C22.9 code can be used for sensitivity analyses. (94% agreement)

11. Ascites may be caused by cirrhosis, but there are other causes of non-hepatic ascites such as heart failure or malignancy. In studies of patients with known chronic liver disease status (such as NAFLD, ALD, or cirrhosis), ascites can be used as a liver-related outcome, but in general in population cohorts, ascites should be combined with coding for chronic liver disease to achieve an acceptable specificity. (94% agreement)

12. Hepatic encephalopathy (HE) does not have a specific code in ICD-10. To define HE, coding for compensated or decompensated cirrhosis can be combined with coding for prescriptions (such as Anatomical Therapeutic Chemical Classification System [ATC] codes) of lactulose or rifaximin to increase specificity, in settings where such data are available. For instance, a person with a diagnosis of cirrhosis and a prescription of rifaximin can be considered as having HE. (78% agreement)

13. Coding for liver failure might represent cirrhosis, but there are alternate causes and specificity might be low. Unless validation studies are performed in the system of the study setting, chronic liver failure codes (ICD-10: K72.1, K72.9) should only be considered as defining cirrhosis in sensitivity analyses, and acute liver failure codes should not be used when defining cirrhosis. (95% agreement)

14. Procedure codes can in general be used to ascertain outcomes related to cirrhosis and can be used alone even if specific coding for cirrhosis is lacking. For example, a case with coding for banding of bleeding esophageal varices, but no formal coding for varices per se, can help define decompensated cirrhosis. However, in contrast to the diagnostic ICD-systems, there are a multitude of different procedure code systems and a list of procedure codes should be defined by the individual research group depending on the setting. (83% agreement)

Procedure codes that could be interesting would depend on the research question. Liver transplantation is a commonly used outcome that can be studied in itself, or as part of a composite outcome. There are certain ICD-codes for the presence of a liver transplant (ICD-10: Z94.4), but procedure coding could also be added to define liver transplantation and would be better to define the date of the transplantation.

Procedures that are strongly associated with cirrhosis include banding or ligation of esophageal or gastric varices, paracentesis, and transjugular intrahepatic porto-systemic shunt placement.

Discussion

We present a comprehensive list of ICD codes that can serve as guidance for future studies of NAFLD when using EHR-data, for instance how to define NAFLD in study cohorts

and how to ascertain progression to cirrhosis. This guidance could be used both when using administrative and clinical databases, as well as upcoming phase 4-studies in the NAFLD/NASH field. Harmonization of definitions will make it easier to compare and contrast study results from different cohorts, leading to an improved understanding of the consequences of NAFLD. These recommendations could also provide guidance for clinicians or administrators responsible for coding disease status in patients with NAFLD.

We also give guidance on some key methodological questions in the field.

However, no guidance can cover all possible research questions or study settings, which is why these recommendations should not be a mandate but rather a suggestion of relevant codes that can be used to define exposure or outcome variables. Some registries/databases might contain more detailed data, such as laboratory data or results from radiology, which allow for more granular definitions than made here. Moreover, some regions may have different coding systems or coding practices so that our recommendations could be irrelevant.

This should not be seen as a complete guide on how to perform research in this field. Different research questions and study settings will require distinct strategies. For instance, examining liver-related outcomes in an EHR-derived general population with unknown NAFLD status is different than examining liver-related endpoints in clinical cohorts with known NAFLD status. EHR-derived population-based cohorts often have a low risk for cirrhosis and have the possibility of having liver diseases other than NAFLD, while the definition of outcomes could be made narrower by combining codes through pre-specified algorithms. An example of this is requiring a code for chronic liver disease when ascites is diagnosed, as there are other causes of ascites apart from cirrhosis, thus risking false-positive findings. This can be compared to EHR-based follow-up studies of persons with known NAFLD, where it is less likely that ascites would be related to competing causes. Again, definitions should be tailored to the specific research question. Also, liver-related outcomes are relatively rare in a general population (26, 27), and consideration of examining more common causes of mortality should be actively considered, depending on the research question.

When assessing the overall impact of NAFLD on clinical liver outcomes in the general population, there is a need to recognize that NAFLD often co-exists with alcohol-related liver disease, and that metabolic risk factors and alcohol use have bi-directional interaction effects on liver disease with in general higher risk for liver-related outcomes in persons with mixed etiologies (28, 29). In such research settings, the exclusion of competing and co-existent causes for liver disease may lead to lower risk estimates associated with NAFLD. For instance, excluding diagnoses of alcohol-related outcomes (ICD-10: K70.3) will reduce the sensitivity of the impact of NAFLD in persons with co-existing NAFLD and ALD, and thought need to be given to the possible co-existence of NAFLD and ALD when designing EHR-based studies depending on the research question. This is true for most use of algorithms using ICD-coding. The requirement of multiple codes to enhance specificity will almost always lead to a lower sensitivity and under-appreciation of the prevalence of the target diagnosis, which should be considered depending on the research question(s).

It should also be acknowledged that NAFLD is severely under-coded in the general population (30, 31), although there are methods to enhance detection of NAFLD in databases with high level of details (32, 33). Consequently, there is often misclassification bias (due to inaccurate coding of subjects in 'control' groups), resulting in attenuation of any association towards the null, but also selection bias (cases diagnosed with NAFLD might be the more severe cases, resulting in inflated risk estimates).

Preferably, validation studies of codes or algorithms used to increase the positive predictive value of the target diagnosis should be undertaken before starting an EHR-based study, if possible. Examples of these are (18, 19, 34). Results of prior validation studies in hepatology in general suggest that while some diagnoses have a high positive predictive value (PPV), there are several non-specific diagnoses where considerations need to be made. An example is ascites which can be found in persons without cirrhosis, but combining coding for ascites with coding for cirrhosis leads to acceptable PPVs (18). Another example is hepatic encephalopathy, where combining drug prescription coding with cirrhosis increases PPVs to acceptable levels (19). One must also take into account the setting where the diagnosis is made. For instance, a diagnosis of "chronic liver failure" made by a hepatologist might have higher validity when compared to the same diagnosis made in a general hospital (18).

Areas of controversy and considerations for future research

Statements where less than 90% of collaborators agreed can be considered to be somewhat controversial and may represent areas for future studies. For instance, how to best classify disease etiology in persons in a general population setting that develop cirrhosis can be difficult when there is no etiological coding, meaning that differentiating between e.g. ALD and NAFLD as the cause of cirrhosis can be difficult.

Similarly, how to deal with study subjects with multiple etiologic codes (e.g. NAFLD and ALD) at different timepoints during study follow-up was considered to be too nuanced and study dependent to make a general recommendation and could be a topic for a future study. As NAFLD is severely under-coded, future studies should also consider how to best use available ICD-coding such as combinations of metabolic syndrome components to achieve an acceptable accuracy for estimation of NAFLD in the general population.

Additionally, full consensus could not be achieved on how to best classify HE in the absence of a specific ICD-code. Some collaborators thought that defining HE by codes for cirrhosis and a prescription code for lactulose risked misclassifying persons where lactulose might be used for primary prevention.

Finally, we chose to limit our discussion to liver-related outcomes, and how to best examine the role of NAFLD in cardiovascular disease using EHR-data remains an open question.

Conclusion

We defined a list of ICD-codes that can be considered by investigators examining NAFLD in electronic healthcare records-based research and reached consensus statements addressing several methodological questions. This guidance is intended to streamline future studies in

this field, leading to increased generalizability of study results, with the aim to improve our understanding of NAFLD prognosis pertaining to liver related outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

AIH	autoimmune hepatitis
ATC	Anatomical Therapeutic Chemical Classification System
ALD	alcohol-related liver disease
EHR	electronic healthcare records
HCC	hepatocellular carcinoma
HE	hepatic encephalopathy
ICD	international classification of diseases
NAFLD	nonalcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
PBC	primary biliary cholangitis
PPV	positive predictive value
PSC	primary sclerosing cholangitis

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Table 1.

List of suggested ICD-codes for versions 8–11 with applicable codes for different diagnoses.

Diagnosis	ICD-8	ICD-9	ICD-10	ICD-11 (version 04/19)
Defining NAFLD at baseline				
NAFLD, all	No available code	571.8	K76.0	DB92.0, DB92.Z DB92.Y
NASH	No available code	No available code	K75.8	DB92.1
Excluding other liver diseases at/before baseline				
ALD	571,00, 571,01	571.0–571.3	K70	DB94
Viral hepatitis	999,2, 070	070	B16, B17, B18, B19	1E50, 1E51, 1E5Z
Autoimmune liver disease (AIH, PBC, PSC)	No available code	571.6, 576.1	K83.0A, K83.0F, K74.3, K75.4	DB96
Hemochromatosis	273,2	275.0	E83.1	5C64.1
Wilson	273,3	275.1	E83.0B	5C64.0
Alpha-1-antitrypsin deficiency	No available code	277.6	E88.0A, E88.0B	5C5A
Budd-Chiari	No available code	453.0	I82.0, K76.5	DB98.5
Chronic hepatitis, unspecified	570	571.4	K73.9, K73.2	DB97.2
Secondary or unspecified biliary cirrhosis	No available code	571.6	K74.4, K74.5	DB93.2
Excluding alcohol/drug use disorder at/before baseline				
Codes associated with alcohol use disorder	303	303, 305.0	F10	6C40
Codes associated with somatic consequences of alcohol (except ALD)	291, 980,00, 980,01, 980,99	291, 357.5, 425.5, 535.3, 980.1, 980.9	E24.4, G62.1, I42.6, K29.2, G31.2, G72.1, K85.2, K86.0, T51.0, T51.9, Y57.3, X65, Z50.2, Z71.4, Z72.1	5A70.2, 8D44.0, 8D44.1, BC43.01, DA42.80, 8A03.30, 8D44.Y, DC31.1, DC32.3, QB95.2, QE10, 6D72.10, DA51.50, 6D84.0
Codes associated with drug use disorders except nicotine/caffeine	No available code	305.1–9	F11-F14, F16, F18, F19	6C41–6C47, 6C4B-H
Compensated cirrhosis				
Cirrhosis, compensated	571,9	571.5	K74.6	DB93.1
Esophageal varices, not bleeding	No available code	456.1, 456.21	I85.9, I98.2	DA26.01, DA26.0Z
Gastric varices, not bleeding	No available code	No available code	I86.4	DA43.0
Decompensated cirrhosis				
Esophageal varices, bleeding	456.0	456.0, 456.20	I85.0, I98.3	DA26.00

Diagnosis	ICD-8	ICD-9	ICD-10	ICD-11 (version 04/19)
Ascites	785.3	789.5	R18	ME04
Hepatic encephalopathy	No available code	572.2	Code for cirrhosis + prescription for lactulose/rifaximin	DB99.5
Hepatorenal syndrome	No available code	572.4	K76.7	DB99.2
Portal hypertension	571,9	572.3	K76.6	DB98.7
Liver transplantation				
Liver transplantation status	No available code	V427	Z94.4	QB63.3
Liver cancer outcomes				
HCC	155,01	155.0	C22.0	2C12.0
Liver cancer, unspecified	No available code	155.2	C22.9	2C12.Z
“Unspecific” codes that might be relevant for some studies				
Chronic or unspecified liver failure	573	572.8	K72.1, K72.9	DB99.7, DB99.8
Acute or subacute liverfailure	570	570	K72.0	DB91
Portal vein thrombosis	No available code	No available code	I81.9, K75.1	DB98.0
Hepatic fibrosis or sclerosis or fibrosis with sclerosis	No available code	571,9	K74.0, K74.1, K74.2	DB93.0

Abbreviations: AIH, autoimmune hepatitis; ALD, alcohol-related liver disease; HCC, hepatocellular carcinoma; ICD, International Classification of Disease; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; PBC, primary biliary cholangitis: PSC, primary sclerosing cholangitis.