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ORIGINAL RESEARCH

Fever of Unknown Origin: A Validation Study of Danish ICD-10 Diagnosis Codes

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Background: Real-world data in form of routinely collected clinical data are a valuable resource for epidemiological research in infectious disease. We examined the validity of a discharge diagnosis of fever of unknown origin from hospital discharge registries.

Methods: We identified patients with a first in- or outpatient diagnosis (primary or secondary) of fever of unknown origin (ICD-10 code R50.0; R50.8, R50.9) recorded in the Danish National Patient Registry (DNPR) between 2010 and 2017 in the North Denmark Region. We based the validation cohort on a mix of patients diagnosed at a highly specialized university department of infectious diseases (n=100), other internal medicine departments (n=50), and patients diagnosed at a regional non-university hospital (n=50). We estimate positive predictive value (PPV) of diagnosis for fever of unknown origin using medical records as reference.

Results: The PPV of a diagnosis of fever of unknown origin for patients diagnosed at the infectious disease department was 61% (95% CI: 51–71%). For other internal medicine departments, it was 14% (95% CI: 6–27%), and for the non-university hospital it was 16% (95% CI: 7–29%). To achieve higher PPVs, we excluded immunocompromised patients, patients who were diagnosed with infection, cancer or rheumatic disease within 7 days after admission, and/or patients with a short hospital stay (maximum 3 days) and no subsequent hospital contact within 1 month. The PPV for diagnoses from the Department of Infectious Diseases improved to 82% (95% CI: 68–91%) for other internal medicine departments it improved to 31% (95% CI: 11–59%), and for the non-university hospital it improved to 36% (95% CI: 13–65%).

Conclusion: We found that only diagnoses made in the Department of Infectious Diseases accurately identified fever of unknown origin, whereas diagnoses made in other units mainly covered infection-related fever, cancer-related fever, or short unspecific fever without further diagnostic work-up.

Keywords: fever of unknown origin, positive predictive value, validation studies

Introduction

Real-world data derived from Danish nationwide medical registries are a valuable data source, allowing researchers to retrieve large and unselected patient cohorts. The Danish National Registry of Patients (DNRP) has captured all hospital discharges for more than 40 years and outpatient contacts for almost 30 years.[1] While the validity and integrity of diagnoses is generally high, any diagnosis code used for research should optimally be validated.

Fever of unknown origin is a challenging diagnosis, describing a syndrome defined using accepted diagnostic criteria but without a classic, clear-cut gold standard of measurement. The condition was first described in 1930,[2] defined with a standard set of criteria in 1960´s,[3] and suggested divided into four groups (classic, nosocomial, HIV-related, and neutropenic) and modified to include outpatient health-care contacts in 1990´s.[4] In 2021, a new definition for fever of unknown origin in the immunocompetent adult patient was proposed: "More than 3 weeks of fever (≥38.0°C) without explanation, despite completing a set of minimal standard diagnostic tests in an immunocompetent patient."[5] In a subsequent review, the authors underlined that although some diagnostic work-up is required, it must not be too rigid and should allow room for subjective evaluation of what "reasonable investigations" and "sufficient time" covers.[6]

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In the Danish International Classification of Diseases 10th (ICD-10) as well as in the American ICD-10-CM codes, several codes could encompass fever of unknown origin (eg "Fever of other or unknown origin", "Other specified fever", and "Fever, unspecified"). The distinction between codes is not straightforward, but in a clinical aspect and for research purposes, there is a vast difference between the condition "fever of unknown origin", and other types of acute febrile illness, such as neutropenic, infection-, or travel-related fever.

To our knowledge, no previous study has examined the validity of diagnosis codes for fever of unknown origin. The aim of this study was to examine the data quality of the ICD-10 diagnosis used for fever of unknown origin in the DNRP, by estimating positive predictive value (PPV) for the diagnosis code using medical chart reviews as references.

Materials and Methods

Danish National Registry of Patients

For this validation study, we used diagnoses registered at Aalborg University Hospital and North Denmark Regional Hospital (catchment area of approximately 600,000). We identified individuals aged 15 years or older in the DNPR[1] with a first in- or outpatient (primary or secondary) diagnosis of fever of unknown origin between January 1, 2010, and December 31, 2017. DNPR records all hospital contacts, including diagnosis codes (using ICD, currently ICD-10). The following ICD-10 codes were used to identify patients: R50.0, R50.8, R50.9. We excluded prevalent cases diagnosed before 2010 (additionally using ICD-8 code 788.89 which was used before 1994).

Validation Cohort

Patients presenting with fever of unknown origin are typically seen by an infectious disease specialist in Denmark. However, in the initial data evaluation, we found that many patients received the diagnosis outside this setting (eg in surgical departments, emergency rooms, etc.). We therefore decided to focus on diagnoses made in three predefined settings: 1) the Department of Infectious Diseases at Aalborg University Hospital (n=100), 2) other internal medicine departments at Aalborg University Hospital (including departments of Hematology, Endocrinology, Cardiology, Gastroenterology, Renal, and Respiratory Diseases) (n=50), and 3) the Department of Clinical Medicine, North Denmark Regional Hospital (regional non-university hospital) (n=50). The index date was the date of hospital admission, or first hospital outpatient contact for fever of unknown origin.

Medical Review

We used available information in electronic patient records, including biochemical, microbiology, and pathology results, as well as imaging examinations from the admission/outpatient contact, in which the diagnosis was made. The medical review was performed by AG (clinical microbiologist), KFK (infectious disease specialist), KKS (clinical microbiologist), and POL (internal medicine specialist). We developed a case report form (CRF) as reference (building on the existing literature)[7,8] and classified patients as having valid, likely, or invalid diagnosis of fever of unknown origin (see Table S1). Patients presenting with prolonged fever (≥38.0 multiple times over a minimum of 3 weeks), with no obvious cause after initial diagnostic workup (including blood tests, blood culture, and imaging) as described under mandatory information in the CRF, were considered valid diagnoses. We allowed for a few exceptions eg not specifically noted that fever had lasted at least 3 weeks or that a few blood tests were missing, provided the clinician used the term "fever of unknown origin", with no evidence of other underlying cause. For patients that clearly had other causes of fever (eg neutropenic, travel-related infection, or bacterial infection), the diagnosis was considered invalid. For patients somewhere in between, ie fever less than 3 weeks, where diagnostics were incomplete but no other obvious cause was found, the diagnosis was considered likely. Those considered likely were counted as valid in the final analysis.

Statistical Analyses

Patient demographics were listed as n (%), and age as median with interquartile range. We calculated the positive predictive value for the diagnosis of fever of unknown origin, by dividing the number of patients with a valid diagnosis (after review) by the number of all patients. Corresponding 95% confidence interval (CI) were calculated using the method for binomial

proportions (Clopper–Pearsons method).[9] It was clear from the initial review of patient records that codes were used broadly for fever (eg neutropenic fever, travel-related fever, and infection-related fever), and we therefore did a stepwise exclusion of patients: 1) immunocompromised patients (defined as cancer, rheumatic disease, and/or treatment with immunosuppressive drugs), 2) a discharge diagnosis of an acute infection, incident cancer, or incident rheumatic disease (concurrent or diagnosed within 7 days after admission), and 3) a short hospital stay (maximum 3 days) and thereafter no subsequent hospital contact within 1 month (since full diagnostic workup for fever of unknown origin was unlikely). Data analyses were performed in STATA (Stata Statistical Software: Release 16.0, StataCorp LLC).

Ethics

The study was approved by the North Region of Denmark (Record no. 2021-032812). Chief physicians approved access to patient records from patients diagnosed in their departments. Patient consent or permission from an ethics committee is not required for this type of study in Denmark.

Results

Descriptive Data

Electronic medical records were available for all 200 patients. The sample included 113 (56.5%) men, and the median age was 59 years (interquartile range 39–71 years). Among the patients, 39 (19.5%) had a prior cancer diagnosis, and 23 (11.5%) were registered with a rheumatic disease diagnosis prior to fever of unknown origin diagnosis or were treated with immunosuppressive medications for other reasons. The diagnosis code most commonly used was R50.9 "Fever, unspecified" (n=177, 88.5%). Patients were sampled evenly across calendar years (Table 1).

Table 1 Descriptive for Fever of Unknown Origin Among 200 Patients Diagnosed at Aalborg University Hospital and North Denmark Regional Hospital, Denmark, 2010–2017

Demographics	**N (%)**
Males	113 (56.5)
Median age year with interquartile range	59 (39–71)
Prior cancer	39 (19.5)
Prevalent rheumatic disease and/or immunosuppressive medication	23 (11.5)
ICD-code	
R50.0 "Fever of other or unknown origin"	<5
R50.8 "Other fever"	<5
R50.8A "Fever with chills"	<5
R50.8B "Persistent fever of unknown origin"	14 (7.0)
R50.9 "Fever, unspecified"	177 (88.5)
Calendar year	
2010	26 (13.0)
2011	28 (14.0)
2012	27 (13.5)
2013	24 (12.0)
2014	30 (15.0)
2015	26 (13.0)
2016	25 (12.5)
2017	14 (7.0)

Validation of Diagnosis of Fever of Unknown Origin

Using the predefined CRF (Table S1), we found that 61 (30.5%) patients were deemed to have a valid diagnosis, 15 (7.5%) had a likely diagnosis, and 124 (62.0%) had an invalid diagnosis of fever of unknown origin. Most valid diagnoses (n=47, 77.0%) were derived from patients diagnosed in the setting of infectious disease specialty, and fewer were diagnosed outside this setting. Fifteen patients with a likely diagnosis did not fulfill all the mandatory criteria (according to the CRF), but were considered valid as the combined clinical evaluation of the patient was in agreement with a diagnosis of fever of unknown origin. Of note, we only found valid diagnoses among patients registered with the ICD-10 codes R50.8B and R50.9.

Positive Predictive Values

The PPV of a diagnosis of fever of unknown origin for patients diagnosed at the infectious disease department was 61% (95% CI: 51–71%), for other internal medicine departments it was 14% (95% CI: 6–27%), and for the non-university hospital it was 16% (95% CI: 7–29%).

When excluding patients with a prior cancer diagnosis, a discharge diagnosis of infection, cancer, or rheumatic disease within 7 days after of admission, as well as patients with a short hospital stay (maximum 3 days), and no subsequent hospital contact within 1 month, the PPV for diagnoses from the infectious disease department improved to 82% (95% CI: 68–91%). For other internal medicine departments and for the non-university hospital it improved to 31% (95% CI: 11–59%) and 36% (95% CI: 13–65%), respectively (Table 2).

Table 2 Validity of ICD-10 Codes for Fever of Unknown Origin Among 200 Patients Diagnosed at Aalborg University Hospital and North Denmark Regional Hospital, Denmark, 2010–2017

	Patients, n	Valid Diagnosis, n	PPV, % (95% CI)
Patients diagnosed at internal medicine departments, Aalborg University Hospital	50	7	14 (6–27)
Stepwise algorithm with exclusion			
Ex. immunocompromised patients* (n=19)	31	5	16 (5–34)
Ex. infection, cancer, or autoimmune disease diagnosis within one week (n=10)	21	5	24 (8–47)
Ex. short admission (max 3 days) and no subsequent hospital contact within one month (n=5)	16	5	31 (11–59)
Patients diagnosed at a North Denmark Regional Hospital	50	8	16 (7–29)
Stepwise algorithm with exclusion			
Ex. immunocompromised patients* (n=20)	30	6	20 (8–39)
Ex. infection, cancer, or autoimmune disease diagnosis within one week (n=11)	19	5	26 (9–51)
Ex. short admission (max 3 days) and no subsequent hospital contact within one month (n=5)	14	5	36 (13–65)
Patients diagnosed at Department of Infectious Diseases, Aalborg University Hospital	100	61	61 (51–71)
Stepwise algorithm with exclusion			
Ex. immunocompromised patients* (n=21)	79	49	62 (50–73)
Ex. infection, cancer, or autoimmune disease diagnosis within one week (n=11)	68	44	66 (52–76)
Ex. short admission (max 3 days) and no subsequent hospital contact within one month (n=20)	49	40	82 (68–91)

Note: *Patients with prior cancer, rheumatic disease, or who are treated with immunosuppressive drugs.

Table 3 Concurrent Diagnoses or Clinically Suspected Disease Among 123 Patients with an Invalid Diagnosis of Fever of Unknown Origin

Concurrent Diagnoses	N (%)
Bacterial infection[a]	52 (41.9)
Viral infection[b]	20 (16.1)
Cancer-related fever[c]	14 (11.3)
Travel-related fever	11 (8.9)
Abdominal infection[d]	7 (5.6)
Cardiac or pulmonary condition[e]	6 (4.8)
Rheumatic or orthopedic disease[f]	4 (3.2)
Other or none[g]	10 (8.0)

Notes: [a]Eg sepsis, UTI, pneumonia, cholecystitis, suspected bacterial infection; [b]Eg CMV, EBV, suspected viral infection; [c]Eg neutropenic fever, new cancer diagnosis; [d]Eg gastroenteritis, inflammatory bowel disease; [e]Eg AFLI, AMI, heart failure, pulmonary embolism, chronic obstructive pulmonary disease; [f]Eg rheumatic disease, fracture, arthrosis; [g]Unspecific symptoms registered in the patient record.
Abbreviations: UTI, urinary tract infection; AFLI, atrial fibrillation; AMI, acute myocardial infarction.

Diagnoses Among Patients Not Fulfilling the Criteria for Fever of Unknown Origin

Among 124 patients deemed to have an invalid diagnosis of fever of unknown origin the majority had a concurrent infection; 52 (41.9%) were diagnosed with a bacterial infection (including cases of bacteremia, urinary tract infection, pneumonia, etc.), 20 (16.1%) had a viral infection (including CMV and EBV, but also more unspecific cases where symptoms resolved spontaneously within days), 11 (8.9%) had travel-related fever, and 7 (5.6%) had gastroenteritis or flares in chronic inflammatory bowel disease. Fourteen (11.3%) patients had cancer-related fever, covering both chemo-related fever, as well as new cancer diagnoses. Few patients (4, 3.2%) had flares in rheumatic disease or an orthopedic injury. Finally, 6 (4.8%) had an acute or chronic cardiac or pulmonary condition (including AMI, pulmonary embolism, chronic obstructive pulmonary disease), and 10 (8.0%) had unspecific symptoms described but no distinct disease registered (Table 3).

Discussion

In this validation study, we found that diagnosis codes for fever do not accurately identify patients with fever of unknown origin. Overall, more than half of the patients had an intelligible cause for their fever episode and as such did not represent patients with fever of unknown origin. However, for patients diagnosed within the setting of infectious diseases with the diagnosis code of "fever, unspecified" (ICD-10 code R50.9), fever of unknown origin could be accurately identified (with a PPV of 82%) when immunocompromised patients, those with concurrent infection, and those with short admission and no subsequent hospital contact within 30 days were excluded.

In 2021, a new definition for fever of unknown origin was proposed by an expert group: "More than 3 weeks of fever (≥38.0°C) despite completing a set of minimal standard diagnostic tests in an immunocompetent patient".[5] Subsequently, in a review, it was more loosely concluded that the core features of the diagnosis are 1) "absence of an identified cause of fever, despite reasonable investigations in either the inpatient or outpatient setting" and 2) "persistence of fever for a sufficient time to rule out self-limiting fevers".[6] This highlights that there are still different opinions on how strict the diagnostic criteria for the condition should be.

We developed a CRF based on the existing literature[7,8] (before the modified approach[5] and review[6] was published) and our common clinical practice in Denmark. We set up mandatory criteria, including several of the newly proposed criteria, though slightly stricter (see Table S1). In our evaluation, it was clear that not all patients with a clinically valid diagnosis of fever of unknown origin fulfilled all our mandatory criteria (based on the CRF). Therefore, some patients initially deemed "likely" were eventually considered valid as the combined clinical evaluation was in agreement with the condition fever of unknown origin. Unfortunately, our available data did not allow for a post hoc analysis strictly using the newly defined diagnostic criteria (because exact data on fever duration was missing in some medical records). However, it would be valuable to compare findings using strict[6] versus less rigid[5] diagnostic criteria in a prospective study.

To our knowledge, no previous study has examined PPV for fever of unknown origin. We evaluated diagnoses made by infectious disease specialists and other internal medicine specialists at both a University Hospital and a regional hospital in Denmark. In Denmark, most patients with this condition will be referred to evaluation by infectious disease specialists. Our findings confirmed that for research purposes in Denmark, only cases diagnosed by infectious disease specialists should be considered, since diagnoses in other settings (in this case internal medicine and regional hospital departments) were found to cover "nosocomial fever" and other known causes of persistent or recurrent fever. Still, to achieve acceptable PPV for research purposes, we needed to set up some additional exclusion criteria. We found a high prevalence of concurrent bacterial and viral infections, in addition to cancer-related fever, and new cancer and autoimmune diseases. Moreover, a substantial part of patients had self-limiting short fever episodes and were discharged within 3 days without further diagnostic follow-up. Using information on co-diagnoses and length of stay from the registries, we achieved a PPV above 80%, which is acceptable for epidemiological research. Our evaluation did not allow for calculation of sensitivity and completeness of fever of unknown origin diagnosis in DNPR, thus the suggested algorithm to correctly identify valid cases of fever of unknown origin may be less appropriate for surveillance and incidence studies. However, for low-prevalence diseases, PPV correlates well with specificity; and a high specificity will result in unbiased relative measures of risk even when the sensitivity is moderate.[10] Accordingly, the validated diagnosis code may be useful in studies of risk and prognosis.

Danish residents have tax-funded access to medical care, covering all expenses related to a hospital admission/outpatient contact and treatment. This tends to minimize the risk of selection bias. The data in DNPR is registered by the treating physician mainly for administrative use, and therefore not related to research questions. Whereas risk of misclassification may exist, recall and nonresponse bias are not an issue.

Our study has some limitations. While there is some overlap between the Danish ICD-10 codes and ICD-10-CM codes (used by member states of the World Health Organization) and terminology within the chapter R50, the coding practices may differ between countries. In Denmark, patients with fever of unknown origin should be coded with R50.9. However, we found that other codes were used and that R50.9 was also used for other causes of fever. We observed that only among patients registered with the ICD-10 codes R50.8B and R50.9 valid diagnoses were present. In comparison, the less frequently used ICD-10 codes R50.0, R50.8, and R50.8A, did not represent valid diagnoses. Accordingly, the diagnosis codes should optimally be validated locally in each country. Moreover, we concluded that only diagnoses made by infectious diseases specialists achieved a PPV acceptable for subsequent research purposes. This may not apply to other countries, where such patients are commonly evaluated and diagnosed by general internal medicine specialists. Finally, given the complexity of the diagnosis, there may be some subjective evaluation of the patients (owing to information provided in the patient records not captured in the CRF).

In conclusion, we found that the diagnosis codes in the ICD-10-chapter R50 for fever of unknown origin alone are not suitable for correctly identifying patients. However, after restriction to patients diagnosed by infectious disease specialists and excluding immunocompromised patients, as well as patients with concurrent infection, and other short self-limiting disease without follow-up diagnostics, the validity of diagnoses was sufficiently accurate. A cohort of patients with valid diagnoses of fever of unknown origin may thus be extracted from DNPR and form the basis for epidemiological studies, examining the prognosis and outcome in this patient group.

Data Permission

The study was approved by the North Region of Denmark (Record no. 2021-032812).

Transparency Declaration

The last author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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