



BMJ Open Detecting transthyretin amyloid cardiomyopathy (ATTR-CM) using machine learning: an evaluation of the performance of an algorithm in a UK setting

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ABSTRACT

Objective The aim of this study was to evaluate the potential real-world application of a machine learning (ML) algorithm, developed and trained on heart failure (HF) cohorts in the USA, to detect patients with undiagnosed wild type cardiac amyloidosis (ATTRwt) in the UK.

Design In this retrospective observational study, anonymised, linked primary and secondary care data (Clinical Practice Research Datalink GOLD and Hospital Episode Statistics, respectively, were used to identify patients diagnosed with HF between 2009 and 2018 in the UK. International Classification of Diseases (ICD)-10 clinical modification codes were matched to equivalent Read (primary care) and ICD-10 WHO (secondary care) diagnosis codes used in the UK. In the absence of specific Read or ICD-10 WHO codes for ATTRwt, two proxy case definitions (definitive and possible cases) based on the degree of confidence that the contributing codes defined true ATTRwt cases were created using ML.

Primary outcome measure Algorithm performance was evaluated primarily using the area under the receiver operating curve (AUROC) by comparing the actual versus algorithm predicted case definitions at varying sensitivities and specificities.

Results The algorithm demonstrated strongest predictive ability when a combination of primary care and secondary care data were used (AUROC: 0.84 in definitive cohort and 0.86 in possible cohort). For primary care or secondary care data alone, performance ranged from 0.68 to 0.78.

Conclusion The ML algorithm, despite being developed in a US population, was effective at identifying patients that may have ATTRwt in a UK setting. Its potential use in research and clinical care to aid identification of patients with undiagnosed ATTRwt, possibly enabling earlier diagnosis in the disease pathway, should be investigated.

INTRODUCTION

Transthyretin amyloid cardiomyopathy (ATTR-CM) is a progressive, fatal disease characterised by the deposition of misfolded transthyretin (TTR) amyloid fibrils in the myocardium which in turn leads to heart

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ The representativeness of Clinical Practice Research Datalink data to the UK general population is well documented, and Hospital Episode Statistics contains data from all National Health Service secondary care activity.
- ⇒ However, findings may not be generalisable to other geographical regions outside of England and the UK.
- ⇒ In the absence of an equivalent diagnosis code for wild type cardiac amyloidosis (ATTRwt) (International Classification of Diseases-10 (ICD-10)-clinical modification) in ICD-10 WHO or Read coding systems, two proxy case definitions were applied—referred to as ‘the definitive cohort’ and ‘the possible cohort’. The small definitive cohort was more precise at detecting positive cases (high precision), but also missed cases (low recall). The larger possible cohort displayed greater uncertainty at detecting positive cases (low precision) but classified a larger population with an ATTRwt diagnosis (high recall).
- ⇒ To refine ATTRwt definitions using diagnosis codes in the UK, patients within the possible cohort who also had a diagnostic code for heart failure with preserved ejection fraction or heart failure with normal ejection fraction were reassigned to the definitive cohort, with a view to improving the recall while maintaining precision.

failure (HF).¹ There are two forms of ATTR-CM: wild-type (ATTRwt), which is associated with ageing, and hereditary (ATTRv), caused by genetic mutations of the *TTR* gene.² Both forms of the disease can be difficult to diagnose due to similarities between ATTR-CM and other causes of HF.¹

ATTRv is rare and thought to affect at least 40 000 people worldwide but its prevalence varies geographically due to the distribution of specific TTR mutations.³ The prevalence of ATTRwt is unknown but emerging data suggest that it is underdiagnosed in routine

practice. For example, evidence from non-invasive cardiac imaging and postmortem examination suggest that ATTRwt may account for up to 13% of HF with preserved ejection fraction (HFpEF) in older patients.^{4,5} The reasons for misdiagnosis or underdiagnosis are multifactorial and include disease, clinician-related and system-related factors,^{2,6} but identifying undiagnosed patients is essential to provide timely and appropriate treatment now that the first disease-modifying therapy for ATTR-CM has been approved.^{7,8}

A non-invasive diagnostic algorithm involving nuclear bone scintigraphy imaging is now standard of care in many countries,^{9–11} and recent consensus recommendations¹ have the potential to increase disease awareness and improve diagnosis rates. However, diagnostic criteria are reliant on a high index of clinical suspicion, which is often lacking and require testing at specialist clinics.

Machine learning (ML) is a branch of artificial intelligence that allows an automated method of identifying patterns and trends in data without having to specify relationships a priori and is particularly useful for multidimensional and dynamic data such as electronic health records (EHRs).^{12,13} ML techniques have been applied across cardiovascular diseases, including the prediction of HF and the detection of cardiac arrhythmias, with promising overall predictive ability.¹⁴ Recently, an ML algorithm was developed to identify undiagnosed ATTRwt in patients with HF using data from a medical claims database in the USA.¹⁵ This algorithm displayed good predictive performance in identifying patients with ATTRwt in the USA. In this study, we sought to evaluate the US ATTRwt ML algorithm in a real-world UK population using EHR from primary care and secondary care.

METHODS

Data sources

This study used primary care data (from the Clinical Practices Research Datalink (CPRD) GOLD data set¹⁶) linked with secondary care data (from the Hospital Episode Statistics (HES) data set¹⁷) in England. The CPRD GOLD database contains anonymised EHR from over 11.3 million patients at 674 general practitioner (GP) practices across the UK and is representative of the UK general population in terms of key demographic and clinical characteristics.¹⁸ HES is a data warehouse of all National Health Service (NHS) secondary care activities in England. HES data was provided by CPRD as a linked data set for patients registered at GP practices in England that participated in the linkage scheme; around 75% of GP practices in England contribute to the CPRD linkage scheme.¹⁸

Study data were obtained from 01 January 2009 to 30 June 2018, including a look-back period from 01 January 2000 to 31 December 2008 to identify pre-existing cases of ATTR-CM. The index date for each patient was the date of their first CPRD/HES record, if this occurred during the study period. For patients whose first CPRD/HES record

occurred during the look-back period, the index date was set to 01 January 2009. Patients were followed-up until the earliest of the following events: transferred out of a GP practice participating in CPRD, GP practice stopped participating in CPRD, death or end of study period.

Machine learning algorithm

The ML (random forest) algorithm was developed using diagnosis codes from the International Classification of Diseases-10 (ICD-10) clinical modification (CM), the codeset used in the USA. The case definition for ATTRwt was derived from ICD-10 CM code E85.82: wild-type transthyretin-related (ATTR) amyloidosis. The ML algorithm mapped a set of data inputs (ICD-10 CM codes), known as features/phenotypes that were present in at least 2% of patients with ATTRwt. There were 1872 features/phenotypes used in the ATTRwt ML algorithm. Features were identified according to the hierarchical structure of the ICD-10 CM classification system, and were categorised at three levels: Subchapter (diagnosis category (eg, I30-I5A—other form of heart disease), Major (diagnosis name (eg, I50 HF)) and Short Description (diagnosis description (eg, I50.84—end stage HF)). A feature was defined as the presence of code from any of the categories (Subchapter, Major or Short Description).

Patient population

Patients were initially eligible for inclusion in the study if they were ≥ 18 years of age on 01 January 2000, had a diagnosis of ATTRwt or HF, had at least one record in either CPRD or HES databases during the study period (01 January 2000 to 30 June 2018), and did not have a diagnosis of primary or amyloid light-chain (AL) amyloidosis. Cohorts were later refined based on the case definition criteria outlined in [table 1](#). In the UK during the study period, data were recorded in clinical practice and diagnoses were coded using Read codes (Clinical Terms V.3; CTV.3) in primary care and ICD-10 WHO 2016 (ie, the WHO 2016 version of ICD-10) codes in secondary care. While a specific ICD-10 CM code for ATTRwt (ie, E85.82) was used in algorithm development using US data, there was no equivalent diagnosis code in the 2016 version of ICD-10 WHO. Therefore, to identify ATTRwt cases, two proxy case definitions were applied; referred to as the definitive cohort and the possible cohort, based on the relative confidence of the respective case definitions. The first iteration of the definitive cohort included patients with senile systemic amyloidosis or senile cardiac amyloidosis, which are alternative terms for ATTRwt (online supplemental table S1).^{19,20} However, to improve recall (identification) of patients in the definitive cohort, patients in the possible cohort who also had a diagnosis code for HFpEF or HF with normal ejection fraction (HFnEF) were reassigned to the definitive cohort in the final iteration ([table 1](#)). The 2016 European Society of Cardiology Guidelines²¹ introduced a new class of HF with mildly reduced ejection fraction, but given this study included data from prior to 2016, this class is not referred

Table 1 Final case definition criteria used in the study

Definitive cohort		Possible cohort
Inclusion codes		
ICD-10 WHO, 2016 version	None	E85.9 - amyloidosis, unspecified I43.1* - cardiomyopathy in metabolic diseases I42.9 - cardiomyopathy, unspecified E85.4 - organ-limited amyloidosis E85.8 - other amyloidosis I42.8 - other cardiomyopathies I42.2 - other hypertrophic cardiomyopathy (non-obstructive) I42.5 - other restrictive cardiomyopathy (constrictive)
Read (CTV.3)	C373D00 - senile systemic amyloidosis C373G00 - senile cardiac amyloidosis	Cyu8L00 -(X)other amyloidosis G558400 - amyloid cardiomyopathy G557000 - amyloid heart disease C373.00 - amyloidosis C373z00 - amyloidosis NOS G557011 - cardiac amyloidosis C373900 - organ limited non-hereditary amyloidosis C373y00 - other specified amyloidosis
Patients in possible cohort with diagnosis code for HFpEF or HFnEF were reassigned to the definitive cohort		
Read (CTV.3)	G583.00 - heart failure with normal ejection fraction G583.11 - HFnEF—heart failure with normal ejection fraction G583.12 - heart failure with preserved ejection fraction	
Exclusion codes (patients with any of the following codes were excluded from the cohorts)		
ICD-10 WHO, 2016 version	None	E85.3 - secondary systemic amyloidosis
Read (CTV.3)	C373C00 - AL amyloidosis C373H00 - amyloid A amyloidosis C373J00 - beta-2 microglobulin amyloidosis C373700 - primary amyloidosis NEC	C373000 - sporadic primary amyloidosis C373500 - secondary amyloidosis
AL, amyloid light chain; CTV3, Clinical Terms V.3; HFnEF, heart failure with normal ejection fraction; HFpEF, Heart failure with preserved ejection fraction; ICD, International Classification of Diseases; NOS, not otherwise specified.		

to further in this manuscript. The true positives are the number of true identifications of people with positive diagnosis and true negative values are the number of true identifications of people with a negative diagnosis. The definitive and possible cohorts are defined by the number of true positives plus the number of false negatives.

Patient and public involvement

As this study did not involve direct patient contact, patients and the public were not involved in the design, conduct, reporting or dissemination plans of the study.

Statistical methods

Matching to a heart failure cohort

To align with the methodology applied in developing the ML algorithm in the USA,¹⁵ the definitive and possible ATTRwt cohorts were each matched in a weighted manner to a non-ATTRwt HF cohort on a 1:1 ratio on age, sex and medical histories as per the original algorithm.¹⁵ The matching process ensured methodological comparability between algorithm development and evaluation.

Conversion from US to UK diagnosis coding classifications

To align between the different coding systems used to develop the algorithm in the USA and evaluate it in the

UK, mapping between the ICD-10 CM and the ICD-10 WHO codes used to derive features was undertaken where possible. Additionally, to account for limited clinical granularity in the UK secondary care coding system compared with the US counterpart, primary care coding was also used to supplement feature derivation. As such, where possible, Read codes were mapped to ICD-10 CM via ICD-10 WHO. To optimise algorithm performance, partial matching was performed on features without a directly corresponding diagnosis code but which were ranked as 1 of the top 50 most clinically important features during algorithm development (ie, most strongly associated with ATTRwt). Due to the methodological constraints of applying an ML algorithm that has already been trained, features that had no complete or partial matches based on UK coding conventions in either primary care or secondary care had to be treated as missing.

Algorithm evaluation

The performance of the algorithm using UK EHR was assessed in the possible and definitive cohorts independently. The methods applied in algorithm development (training and testing, ie, 1:1 matching) were also used in this study to ensure comparability with published

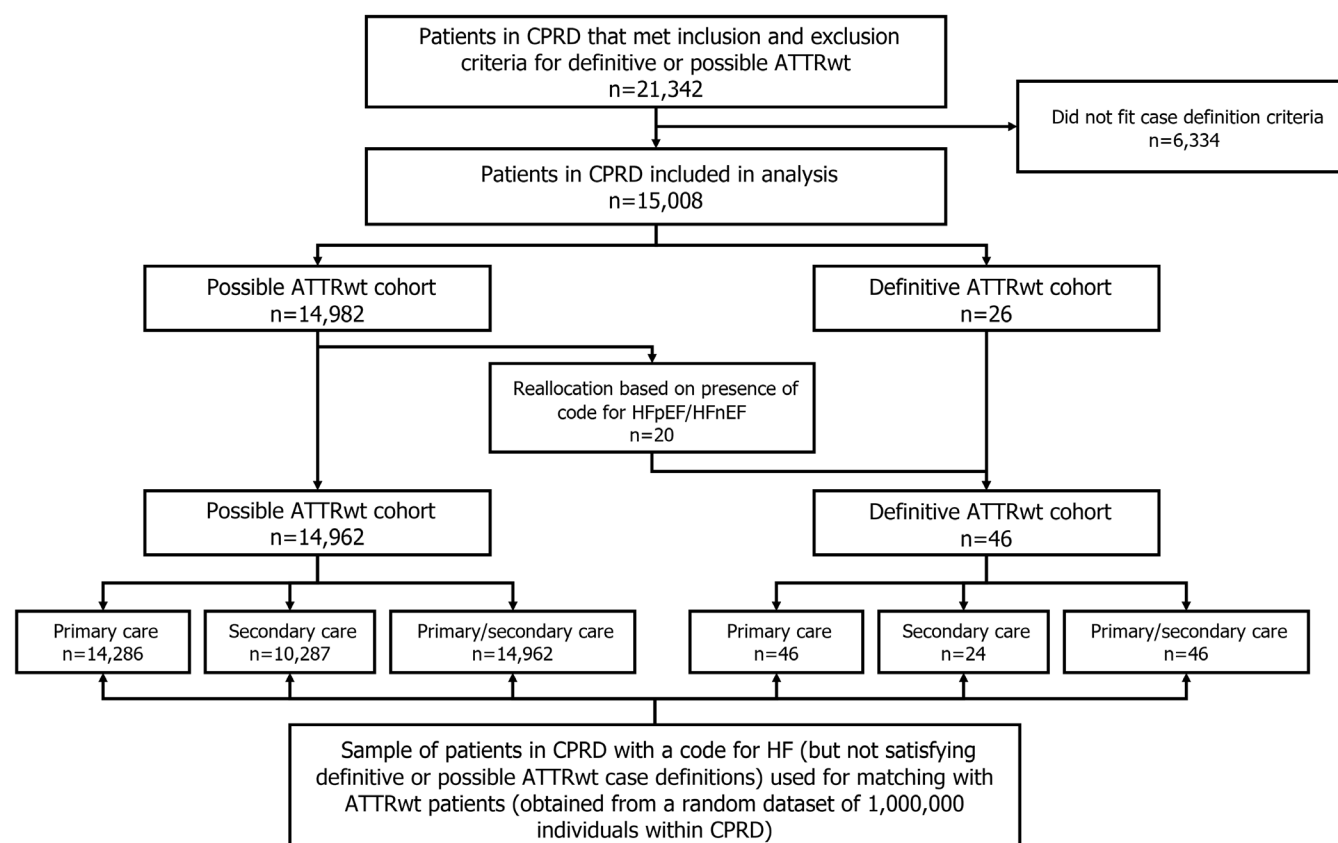


Figure 1 Derivation of patient numbers included in each cohort. ATTRwt, wild-type transthyretin amyloid cardiomyopathy; CPRD, Clinical Practice Research Datalink; HF, heart failure; HFnEF, HF with normal ejection fraction; HFpEF, HF with preserved ejection fraction.

evidence on the algorithm's performance.¹⁵ Features were considered present if they were recorded (ie, by the presence of a diagnosis code) between the index date and the end of the study period (30 June 2018). In line with algorithm training, time-dependency was not considered. A single risk score was produced for each patient with ATTRwt (ie, positive diagnosis) and also their matched equivalent (ie, negative diagnosis). Algorithm performance was evaluated primarily using the area under the receiver operating curve (AUROC), by comparing the actual versus algorithm predicted case definitions at varying sensitivities and specificities. Sensitivity, specificity, positive predictive value and negative predictive value were also assessed at a predefined sensitivity level, as was algorithm accuracy, calculated as the sum of true positives and true negatives divided by the sample size

RESULTS

Patient characteristics

The definitive ATTRwt cohort consisted of 46 patients; all 46 patients had primary care data included in the analysis and 24 patients had linked secondary care data (figure 1). The possible ATTRwt cohort was much larger; of the 14962 patients in the overall cohort, 14286 had primary care data included in the analysis and 10287 had

secondary care data. Regardless of the care setting used to derive case definitions, the definitive cohort was on average older than the possible cohort (range: 76.2–77.8 years vs 69.0–70.0 years) and both cohorts showed a male predominance (range: 54.2–65.2%; table 2).

Based on primary care and linked secondary care data, patients in the definitive cohort were more likely to have HF (34.9%) and atrial fibrillation (AF) (21.7%) compared with the possible cohort (21.7% and 15.8%, respectively), but had a similar prevalence of hypertension; 17.4% of the definitive and 20.2% of the possible cohort had hypertension. Medication usage was generally more prominent in the definitive cohort regardless of data source; only angiotensin II antagonists (range: 11.3–12.2%) were more common in the possible cohort. The characteristics of patients in the first iteration of cohort definitions (ie, before the reassignment of patients with HFpEF/HFnEF) are shown in supplementary material (online supplemental table S2).

Feature set mapping

Of 1872 features in the original algorithm,¹⁵ 63.9% (n=1184) were mapped using a combination of diagnosis codes from primary care and secondary care. Some features had a greater impact on the algorithm's predictive ability than others, which was quantified in terms of

Table 2 Characteristics of patients with ATTRwt

	Primary care only		Secondary care only		Primary care and linked secondary care	
	Definitive cohort (n=46)	Possible cohort (n=14 286)	Definitive cohort (n=24)	Possible cohort (n=10 287)	Definitive cohort (n=46)	Possible cohort (n=14 962)
Demographic characteristics						
Age (years)						
Mean (SD)	76.2 (12.4)	69.0 (14.6)	77.8 (14.9)	70.0 (14.9)	76.2 (12.4)	69.3 (14.7)
Median (IQR)	78 (71–85)	71 (59–81)	81 (69–89)	72 (60–82)	78 (71–85)	71 (59–81)
Range	40–97	37–111	40–97	37–111	40–97	37–111
Female, n (%)	16 (34.8)	5316 (37.2)	11 (45.8)	3898 (37.9)	16 (34.8)	5551 (37.1)
Ethnicity, n (%)						
White	10 (21.7)	2721 (19.0)	*	1863 (18.1)	10 (21.7)	2753 (18.4)
Black, Asian and other	12 (26.1)	2281 (16.0)	*	1703 (16.6)	12 (26.1)	2306 (15.4)
Unknown	24 (52.2)	9284 (65.0)	13 (54.2)	6721 (65.3)	24 (52.2)	9903 (66.2)
Clinical measurements, mean (SD)						
BMI (m/kg ²)	23.9 (7.1)	29.4 (7.0)	27.0 (8.3)	29.1 (7.0)	23.9 (7.1)	29.4 (7.0)
DBP (mm Hg)	70.7 (14.1)	76.0 (12.3)	72.1 (13.1)	75.8 (12.2)	70.7 (14.1)	76.0 (12.3)
SBP (mm Hg)	123.4 (29.6)	127.6 (19.8)	131.7 (29.7)	127.5 (19.4)	123.4 (29.6)	127.6 (19.8)
Troponin I (ng/L)†	–	59.8 (61.1)	–	77.7 (60.6)	–	59.8 (61.1)
Troponin T (ng/L)†	–	43.1 (45.9)	–	72.9 (61.0)	–	43.1 (45.9)
Comorbidities (on index date), n (%)						
Cardiomyopathy‡	18 (39.1)	8448 (59.1)	10 (41.7)	6314 (61.4)	18 (39.1)	8907 (59.5)
Hypertension	8 (17.4)	2860 (20.0)	6 (25.0)	2806 (27.3)	8 (17.4)	3023 (20.2)
Heart failure	16 (34.9)	3114 (21.8)	8 (33.3)	2436 (23.7)	16 (34.9)	3249 (21.7)
Arrhythmia	10 (21.7)	2605 (18.4)	6 (25.0)	2428 (23.6)	10 (21.7)	2774 (18.5)
Coronary artery disease	*	1857 (13.0)	*	1726 (16.8)	*	1968 (13.2)
Shortness of breath	*	1294 (9.0)	*	904 (8.8)	*	1325 (8.8)
Atrial fibrillation	10 (21.7)	2235 (15.6)	6 (25.0)	2078 (20.2)	10 (21.7)	2372 (15.8)
Chronic kidney disease	*	709 (5.0)	*	638 (6.2)	*	742 (5.0)
Angina	*	582 (4.1)	*	598 (5.8)	*	618 (4.1)
Medication, n (%)						
ACE inhibitor	22 (47.8)	5347 (37.4)	8 (33.3)	3260 (31.7)	22 (47.8)	5352 (35.8)
Beta-blocker	24 (52.2)	5818 (40.7)	13 (54.2)	3629 (35.3)	24 (52.2)	5828 (39.0)
Loop diuretic	23 (50.0)	4223 (29.6)	13 (54.2)	2661 (25.7)	23 (50.0)	4229 (28.3)
Anticoagulant	15 (32.6)	2692 (18.8)	7 (29.2)	1738 (16.9)	15 (32.6)	2697 (18.0)
Vasodilator	5 (10.9)	1069 (7.5)	*	708 (6.9)	5 (10.9)	1069 (7.1)
Aldosterone antagonist	10 (21.7)	2248 (15.7)	*	1387 (13.5)	10 (21.7)	2251 (15.0)
Nitrates	5 (10.9)	1037 (7.2)	*	686 (6.7)	5 (10.9)	1037 (6.9)
Angiotensin II antagonist	*	1744 (12.2)	*	1165 (11.3)	*	1747 (11.7)

*Cells containing <5 events have been suppressed in accordance with Clinical Practices Research Datalink requirements.

†No patients in the definitive cohort had a troponin T/I measurement.

‡Includes: dilated, hypertrophic, restrictive, infiltrative cardiomyopathies. Note: there was no diagnostic code for transthyretin amyloid cardiomyopathy at the time of the study.

ATTRwt, wild-type transthyretin cardiac amyloidosis; BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure.

feature importance. Approximately 75% of the cumulative importance of features in the algorithm was derived from the top 50 ranked features. Examples of the top ranked features that were predictive of ATTRwt included primary and secondary intrinsic cardiomyopathies, carpal tunnel syndrome and HFpEF.¹⁵ When adjusting for only the features that were matched to the UK coding system, this accounted for approximately two-thirds of the feature importance. There was no relationship between mapping coverage and feature importance, features that were matched or not matched were distributed across the entire feature importance spectrum. The rate of manual partial matching of the key non-matched codes was very low, at approximately 0.5%.

Algorithm performance in a UK setting

Algorithm performance was assessed in six scenarios: using primary care only, secondary care only and linked primary and secondary care data, in the possible and definitive cohorts. The performance statistics are outlined in table 3 and the receiver operating curves visualised in figure 2. In a previous study using US claims data from IQVIA and Optum EHR data, the algorithm achieved strong predictive performance (AUROC: 0.95 in both cohorts).¹⁵ In this evaluation study using UK EHR, performance metrics were lower than achieved with US data.¹⁵

In the possible cohort, there was no difference in performance when primary care only data or secondary care only data were used (AUROC: 0.78). The algorithm performance was higher when data from both settings was used (AUROC: 0.86). Figure 2 shows that the algorithm performed accurately in predicting cases (or non-cases) across varying sensitivities and specificities. When primary care data only were used, the algorithm performed well at high specificity (true negative rate), possessing the ability to distinguish a large proportion (~50%) of true cases despite a high specificity threshold. Conversely, when using secondary care data only, the algorithm was less able to distinguish true cases at high specificities but outperformed its use with primary care data in all scenarios where sensitivity was greater than 0.7.

When running the definitive cohort and matched equivalents through the ML algorithm, there was generally a small reduction in performance relative to the possible cohort. Using both primary care data with linked secondary care data, the algorithm was able to differentiate accurately between true and false negative cases using the relative features across the two data sources, achieving the best performance (AUROC: 0.84 vs 0.68–0.79). Using secondary care data only, there was little difference in algorithm performance between the definitive cohort (AUROC: 0.79) and the possible cohort (AUROC: 0.78). Across all scenarios, relative performance in the definitive cohort was penalised due to the low level of recall associated with this cohort and uncertainty surrounding the performance statistics given the small patient numbers involved. Results for the first iteration of cohort definitions (ie, no reassignment of HFpEF/HfnEF) are shown

Table 3 Algorithm performance (summary statistics) by UK case definitions

	Primary care only	Secondary care only	Primary care and linked secondary care
Definitive cohort			
N	91	69	92
True positives	30	16	31
True negatives	26	32	38
False positives	19	8	8
False negatives	16	13	15
TPR (sensitivity)	0.65	0.67	0.67
TNR (specificity)	0.58	0.71	0.89
PPV	0.61	0.55	0.79
NPV	0.62	0.80	0.72
Accuracy*	0.62	0.70	0.75
AUROC	0.68	0.79	0.84
Possible cohort			
N	28 841	23 724	29 924
True positives	9525	6858	9969
True negatives	11 049	9845	13 377
False positives	3506	3592	1585
False negatives	4761	3429	4993
TPR (sensitivity)	0.67	0.67	0.67
TNR (specificity)	0.76	0.74	0.89
PPV	0.73	0.66	0.86
NPV	0.70	0.74	0.73
Accuracy*	0.71	0.70	0.78
AUROC	0.78	0.78	0.86
*Accuracy should be interpreted with caution as it assumes that correct prediction of a positive case is equally important as correct prediction of a negative case, and that the number of positive and negative cases are similar or equal. AUROC, area under the receiver operating characteristics; NPV, negative predictive value; PPV, positive predictive value; TNR, true negative rate; TPR, true positive rate.			

in the supplementary material (online supplemental table S3 and figure S1).

DISCUSSION

This study evaluated an ML algorithm for identifying ATTRwt in the UK using EHR from primary care, secondary care and a combination of records from both healthcare settings. The algorithm performed well in a UK setting using UK data, although performance was poorer than that achieved using US claims data from IQVIA and Optum EHRs. AUROCs of 0.84 and 0.86 were achieved

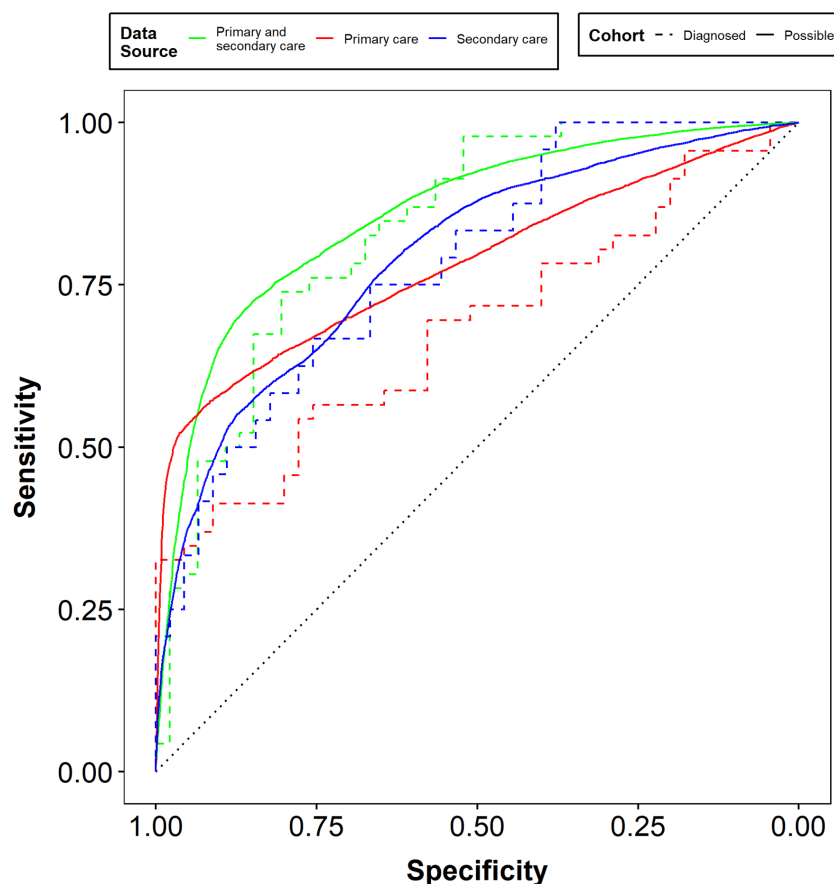


Figure 2 Receiver operating curves: Algorithm performance of UK case definitions.

for primary care and linked secondary care records for definitive and possible cohorts, respectively. Using UK data, the algorithm displayed strongest predictive ability when using a combination of primary care and secondary care data, given the ability to draw from features across both healthcare settings. This study is the first to evaluate an ML algorithm using EHR only to identify ATTRwt in the UK.

ATTR-CM is frequently overlooked as a cause of HF and is often delayed in its recognition. In the UK, the average diagnostic delay in patients with ATTRwt from first presentation with cardiac symptoms is 39 months.²² Some 40% of patients with ATTRwt wait more than 4 years for a diagnosis. By the time a diagnosis is made, many patients will have progressed to advanced HF, missing any opportunity for early intervention to alter the course of the disease. The reasons for missed and delayed diagnosis are multifactorial and include the previously perceived rarity of the disease, overlap of symptoms with other conditions, fragmented knowledge and the heterogenic and multi-systemic nature of the disease.² Identifying undiagnosed patients is key to provide timely and appropriate treatment, especially as the first disease-modifying therapy for ATTR-CM has been approved.^{7,8}

To aid in the diagnosis of ATTR-CM, a non-invasive diagnostic algorithm for ATTR-CM has been recently published.⁹ However, effective use of this diagnostic

algorithm requires a high degree of clinical suspicion, specialist consultations and patient testing at specialist clinics. Similarly, a set of ‘red flag’ markers designed to assist in the diagnosis of ATTR-CM among patients with HF have recently been proposed, including a combination of both cardiac and non-cardiac conditions.² However, many of these ‘red flags’ are common in older individuals and their presence does not necessarily indicate individuals will develop ATTR-CM. Consequently, screening for ATTR-CM using this framework may be too broad and result in overscreening.

Alternatively, ML may offer an enhanced approach in identifying potential ATTRwt cases through the detection of patterns between clinical variables before patients enter the existing diagnostic route.²³ Use of the ML algorithm may aid in identifying an initial high-risk cohort that would warrant in-depth evaluation and confirmation of ATTRwt, leading to earlier treatment for these patients. The ML algorithm may be useful in a clinical setting, as it would increase the suspicion of ATTRwt in patients with HF, prompting clinicians to conduct confirmatory non-invasive diagnostic testing (eg, bone scintigraphy). The ML algorithm has broad applicability, as it is able to use Read and ICD-10 WHO codes which are important classifications for primary and secondary care in the UK. Further work would be required to map to SNOMED CT codes for applicability in current clinical

practice. Diagnosis and clinical recognition of ATTRwt remains important due to high morbidity and mortality associated with the disease.

While there is commonality in the gold-standard methods of ATTR diagnosis between the USA and UK,⁹ coding practices between the two countries vary significantly, which affects the coverage of features derived from US data within UK coding systems. Despite this, the ATTRwt ML algorithm developed using US claims data from IQVIA and Optum EHR data performed well in the UK setting. However, there were differences in the characteristics of patients with ATTRwt identified in this study (definitive cohort) and previously reported cohorts. In our study, the proportion of men was 55–65%, yet Huda *et al*¹⁵ and other studies^{22 24 25} have indicated a much stronger male predominance of ATTRwt of 80–90%. Furthermore, the prevalence of comorbidities including hypertension, coronary artery disease and AF in our definitive cohort were approximately one quarter to one-third that of the prevalence reported in the US cohorts used in algorithm development and validation.¹⁵ The proportion of patients with HF was also lower than expected (<35% across UK cohorts), considering ATTR-CM is a strongly associated cause of HF. A possible explanation is that the definitive cohort was identified using primary care codes, therefore a bias may have occurred towards individuals with less progressed ATTRwt who were less likely to have HF than those hospitalised.

Differences in clinical phenotype were also present between the definitive and possible cohorts in our study. Patients in the possible cohort were younger, more likely to be overweight, less likely to have HF and AF, but more likely to have coronary artery disease and generally were in receipt of fewer medications than the definitive cohort. Approximately 50% of the definitive cohort received ACE inhibitors, beta-blockers or loop diuretics. These medications may be poorly tolerated in patients with ATTR-CM,²⁶ further highlighting the need for timely diagnosis to avoid inappropriate treatment. Patient numbers in the definitive cohort were small and the comparisons in clinical phenotype between the US ATTRwt cohorts and the UK possible cohort should also be interpreted with caution.

A key limitation of the study was the lack of an equivalent diagnosis code for ATTRwt (ICD-10-CM) in ICD-10 WHO or Read coding systems arising from differences in coding practices between the USA and UK. Further, there are differences between the UK and US healthcare systems that affect data entry, and thus availability and quality for research beyond simply that different coding systems are used. Due to lack of an equivalent diagnosis code to identify ATTRwt cases in this study, two proxy case definitions were applied; referred to as the definitive cohort and the possible cohort based on the relative confidence of the respective case definitions. The possible cohort was larger, but uncertainty in true ATTRwt diagnosis was greater (ie, high recall, low precision). To refine ATTRwt definitions using diagnosis codes

in the UK, patients within the possible cohort who also had a diagnostic code for HFpEF or HFnEF were re-assigned to the definitive cohort. This step aimed to address the key limitation of the definitive cohort, specifically the low levels of recall while retaining precision using known relationships between HFpEF and HFnEF and the condition of interest.^{5 25} However, across all scenarios, relative performance in the definitive cohort was still penalised due to the low level of recall associated with this cohort and uncertainty surrounding the performance statistics given the small patient numbers involved. How well these case definitions reflect the known ATTRwt population in the UK requires further validation. The National Amyloidosis Centre (NAC) is situated at the Royal Free Hospital in London and provides diagnostic and management advice services for the national case load of patients with ATTR-CM. The NAC diagnosed more than 600 new patients with ATTRwt between 2000 and 2017²² compared with 46 patients with ATTRwt in the UK in our data set (definitive cohort) during the study period (2000–2018). This discrepancy in actual versus observed numbers highlights coding inadequacies in secondary care, notably the lack of specific disease codes for ATTRwt.

Only 58% of GP practices that contribute to the CRPD GOLD database are linked with HES,¹⁸ meaning there was incomplete linkage with secondary care records in our study data set. This may have been associated with a biased study population, as the CPRD data set may not be representative of all GP practices and their registered patients in the UK, especially as linkage between CPRD and HES was only possible for GP practices in England. CPRD and HES contain data that are routinely collected as part of clinical care, and therefore analyses and interpretation of results are dependent on the quality and completeness of original data entry. However, both data sources are used for NHS payments and reimbursements, the representativeness of CPRD data to the UK general population is well documented and HES contains data from all NHS secondary care activity.^{17 18}

CONCLUSION

ATTRwt is a condition that is often underdiagnosed and misdiagnosed leading to diagnostic delay.^{2 6} As such, patients, their families and healthcare services may incur increased burden during extended contact associated with diagnostic investigations.^{22 27 28} Furthermore, delays in ATTRwt diagnosis are associated with more advanced disease at diagnosis.^{27 29} The findings from this study indicate that the ML algorithm may aid prompt identification of patients with undiagnosed ATTRwt in clinical practice, enabling patients to be diagnosed at an earlier stage in the disease pathway. Beyond this first step of evaluating the ML algorithm in a UK setting, prospective research is required to further investigate the applicability of the algorithm in real-world UK clinical care.

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Competing interests CT is a full-time employee of Pfizer but was employed by HEOR during the study. AH is a full-time employee of Pfizer. JB was a full-time employee of Pfizer during the study. VL was a paid contractor of Pfizer in connection with development of this manuscript. MN and CD are employees of Health Economics and Outcomes Research (HEOR). HEOR received fees from Pfizer in relation to this study. MM received funding for consulting services from Pfizer during preparation of this manuscript. PE received funding for consulting services from Pfizer during preparation of this manuscript and received consulting fees from Pfizer, Novo Nordisk, BMS, Sanofi, DinaQor, Sarepta, Freeline and AstraZeneca.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval The study was approved by the Independent Scientific Advisory Committee (ISAC) of the Medicines and Healthcare products Regulatory Agency (protocol number 19_013R). The CPRD has been granted generic ethics approval for observational studies that make use of only anonymised data and linked anonymised NHS healthcare data (Multiple Research Ethics Committee ref. 05/MRE04/87). This work uses data provided by patients and collected by the NHS as part of their care and support.

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