Implementing a Machine-Learning-Adapted Algorithm to Identify Possible Transthyretin Amyloid Cardiomyopathy at an Academic Medical Center

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ABSTRACT

BACKGROUND: Wild-type transthyretin amyloid cardiomyopathy (ATTR-CM) is a frequently under-recognized cause of heart failure (HF) in older patients. To improve identification of patients at risk for the disease, we initiated a pilot program in which 9 cardiac/non-cardiac phenotypes and 20 high-performing phenotype combinations predictive of wild-type ATTR-CM were operationalized in electronic health record (EHR) configurations at a large academic medical center.

METHODS: Inclusion criteria were age >50 years and HF; exclusion criteria were end-stage renal disease and prior amyloidosis diagnoses. The different Epic EHR configurations investigated were a clinical decision support tool (Best Practice Advisory) and operational/analytical reports (Clarity™, Reporting Workbench™, and SlicerDicer); the different data sources employed were problem list, visit diagnosis, medical history, and billing transactions.

RESULTS: With Clarity, among 45,051 patients with HF, 4006 patients (8.9%) had ≥1 phenotype combination associated with increased risk of wild-type ATTR-CM. Across all data sources, 2 phenotypes (cardiomegaly; osteoarthrosis) and 2 combinations (carpal tunnel syndrome + HF; atrial fibrillation + heart block + cardiomegaly + osteoarthrosis) generated the highest proportions of patients for wild-type ATTR-CM screening.

CONCLUSION: All EHR configurations tested were capable of operationalizing phenotypes or phenotype combinations to identify at-risk patients; the Clarity report was the most comprehensive.

KEYWORDS: All EHR configurations tested were capable of operationalizing phenotypes or phenotype combinations to identify at-risk patients; the Clarity report was the most comprehensive.

Introduction

Wild-type transthyretin amyloidosis with cardiomyopathy (ATTR-CM) is a progressive, life-threatening disease caused by age-related formation of transthyretin amyloid fibrils that accumulate in the myocardium and other organs and tissues.¹ This disease is an increasingly recognized cause of heart failure (HF), with estimated rates of 7% to 20% reported among patients admitted to the hospital with HF and preserved ejection fraction and/or increased ventricular wall thickness screened by radionuclide scintigraphy or biopsy.² ³ Despite enhanced awareness, wild-type ATTR-CM is often misdiagnosed or diagnosed late in the disease course as patients’ HF is misattributed to more common causes, such as hypertension or renal disease.⁴ ⁵ Availability of the disease-modifying therapy tafamidis, which substantially reduces the risk of all-cause mortality and cardiovascular-related hospitalization in variant and wild-type ATTR-CM, underscores the clinical importance of timely diagnosis and treatment, especially given that the greatest benefit is observed in early-stage disease.⁷

The deposition of amyloid in patients with wild-type ATTR-CM is systemic and not limited to the heart, with multiorgan involvement leading to clinical manifestations such as carpal tunnel syndrome, lumbar stenosis, kidney disease, and neuropathy of varying severity.¹ In some patients, non-cardiac manifestations such as carpal tunnel syndrome may develop many years before the onset of HF or other cardiac-related manifestations.⁸ Such non-cardiac comorbidities provide clinical clues for the identification and early diagnosis of ATTR-CM, resulting in improved management and greater benefit.⁹ However, no proven clinical decision support (CDS) or reporting tools that factor in the multiple comorbidities currently exist for application within healthcare system databases or at the point of care to identify patients at high risk for ATTR-CM.
As an initial step in a complex research pathway to create such tools, a machine learning (ML) prediction model was developed for identifying phenotypic patterns indicative of cardiac amyloidosis using International Classification of Diseases (ICD) diagnosis codes in US medical claims data from IQVIA and electronic health record (EHR) data from Optum. The model was shown to successfully identify wild-type ATTR-CM in patients with HF with high sensitivity, specificity, and accuracy in these large, nationally representative databases: 87%/87%/87%, respectively, in IQVIA, and 90%/79%/84%, respectively, in Optum. Consistent model performance was shown in further testing in a retrospective, case-control study using external real-world datasets from 2 large academic medical centers. The original ML algorithm was subsequently modified to include 11 selected phenotypes, and tested and validated in IQVIA medical claims and Optum EHR datasets. The robust performance of this revised model in classifying patients with wild-type ATTR-CM versus non-amyloid HF, demonstrated by sensitivity, specificity, and accuracy rates of 77%/72%/74% (IQVIA) and 72%/65%/68% (Optum), suggest that this framework may serve as a potential tool to help identify patients at risk for wild-type ATTR-CM in a real-world clinical setting.

We describe the practical implementation steps for using an ML-adapted model—for real-time CDS and for reporting—to assess its viability in a clinical setting. We compared the numbers of patients identified using select phenotypes across different EHR configurations as well as across different data sources within the EHR clinical chart and non-EHR billing transactions to better understand the feasibility of using such processes to identify patients at increased risk for wild-type ATTR-CM in a real-world clinical setting.

**Methods**

**EHR configurations**

Two configuration options within the Epic EHR system (Verona, WI) were developed and implemented to ascertain practicality and clinical integration. Specifically, the ML-derived predictive combinations were implemented as: (1) a silent CDS alert in the background using Epic’s Best Practice Advisory, (2) operational and analytical reports using Clarity™, Reporting Workbench™, and SlicerDicer (Figure 1).

A CDS alert can be used to identify patients who meet specific clinical, demographic, or administrative criteria and to notify the physician treating the patient in real time. The CDS in our study was set to run silently in the background during our testing. Reports, both operational and analytical, are used for the similar purpose of identifying patients who satisfy predetermined criteria. Reporting Workbench, an operational report in Epic, is used to generate a list of patients in a particular clinic who meet the indicated criteria either for that specific day or over a longer period of time. Clarity and SlicerDicer provide analytical reports that can assess patients within the entire hospital system. SlicerDicer is primarily used for generating counts (eg, the number of patients meeting specified criteria over the past year), while Clarity can provide more robust data, including patient identifiers and their demographics,
diagnoses, procedures, and other information stored in the electronic health system.

EHR implementation approaches for the high-performing phenotype combinations were developed based on operational and workflow alignment. A series of technical instructions was created and followed when developing both the CDS and reports for patient inclusion/exclusion criteria and high-performing phenotype combinations. An iterative process was followed for alert and report development and testing within the EHR.

For each EHR configuration, different data sources within, or produced by, the EHR were employed and assessed for functional quality. Three data sources were from the EHR (problem list, visit diagnosis, and medical history) and 1 data source was from non-EHR invoicing data (billing transactions).

**Patient criteria, phenotypes, and phenotype combinations**

Data were derived via the Epic EHR system for patients who had received care at the academic medical center or an affiliated hospital/clinic. Patients were >50 years of age and had diagnostic codes for HF (ICD-10 codes I50–E85; active or resolved), but they did not have codes for end-stage renal disease or amyloidosis (Table 1). The local university and medical center Institutional Review Boards classified the study as exempt from further review or approval, waiving informed consent, as all data were de-identified after derivation.

From the original validated random forest ML model for identification of patients with wild-type ATTR-CM, clinical

| PATIENT INCLUSION/EXCLUSION CRITERIA | PHENOTYPES | PHENOTYPE COMBINATIONS |
|-------------------------------------|------------|------------------------|
| • Age >50 years                     | • Cardiac-related phenotypes | • Atrial fibrillation/flutter plus: |
| • Heart failure diagnosis (active/resolved) | 1. Atrial fibrillation/flutter | 1. Cardiomegaly + CKD + joint disorder |
| • No end-stage renal disease diagnosis | 2. Cardiomegaly | 2. Cardiomegaly + CKD + joint disorder + osteoarthritis |
| • No amyloidosis diagnosis, that is, none of the following: | 3. Cardiomegaly | 3. Cardiomegaly + CKD + soft tissue disease |
| o Light chain amyloidosis            | 4. Cardiomegaly + joint disorder + soft tissue disease | |
| o Cerebral amyloid angiopathy        | 5. Cardiomegaly + joint disorder + osteoarthritis + pleurisy or pleural effusion |
| o Amyloidosis/other amyloidosis/ unspecified amyloidosis | 6. Cardiomegaly + joint disorder + osteoarthritis |
| o Secondary systemic amyloidosis     | 7. Heart block + cardiomegaly + osteoarthritis |
| o Organ-limited amyloidosis          | 8. Heart block + joint disorder |
| o Wild-type transthyretin–related amyloidosis | • Cardiomegaly plus: |
| o Non-neuropathic/neuropathic/ unspecified heredofamilial amyloidosis | 9. Carpal tunnel syndrome |
| • Cardiac-related phenotypes         | 10. CKD + joint disorder + soft tissue disease |
| 1. Atrial fibrillation/flutter       | 11. Joint disorder + osteoarthritis + pleurisy or pleural effusion |
| 2. Cardiomegaly                     | • Heart block plus: |
| 3. Heart block                      | 12. Cardiomegaly + CKD + osteoarthritis |
| • Non-cardiac-related phenotypes    | 13. Cardiomegaly + joint disorder |
| 4. Carpal tunnel syndrome           | 14. Cardiomegaly + joint disorder + osteoarthritis |
| 5. CKD                              | 15. Cardiomegaly + soft tissue disease |
| 6. Joint disorder                   | 16. CKD + joint disorder |
| 7. Osteoarthritis                   | 17. Joint disorder + osteoarthritis |
| 8. Pleurisy or pleural effusion     | 18. Joint disorder + soft tissue disease |
| 9. Soft tissue disease              | • Carpal tunnel syndrome plus: |
| • Atrial fibrillation/flutter plus: | 19. —b |
| 1. Cardiomegaly + CKD + joint disorder | 20. CKD |

Abbreviations: ATTR-CM, transthyretin amyloid cardiomyopathy; CKD, chronic kidney disease; EHR, electronic health record.

aIncludes enthesopathy, non-traumatic tendon rupture, and strains or sprains.

bCombined with patient inclusion criteria.
features (ICD codes) were derived and mapped to clinically relevant phenotypes.9,12 The strength of association of the individual phenotypes with wild-type ATTR-CM versus non-amyloid HF was compared using logistic regression analyses to calculate odds ratios (95% CI). For the current analyses, 9 high-performing cardiac and non-cardiac phenotypes with odds ratios in the highest tertile for prediction of wild-type ATTR-CM were selected (Table 1). These ML model-adapted phenotypes were grouped into 20 combinations, comprised of up to 5 phenotypes each, based on odds ratios and performance characteristics, and linked with the above-mentioned patient inclusion/exclusion criteria.

**EHR configuration testing**

A silent version of the CDS notification was deployed in March 2020 to capture patients who satisfied the inclusion and exclusion criteria and had at least 1 of the 20 combinations (Table 1). After 6 weeks of running the CDS notification in the background, reports were generated to assess the impact of the EHR configurations, various data sources, and phenotype combinations on the identification of patients at possible risk for wild-type ATTR-CM within the EHR. The performance duration of each configuration, designed for different purposes, varied for pragmatic reasons from 6 weeks (Best Practice Advisory and Reporting Workbench) to 2 years (Clarity) and 3 years (SlicerDicer). Reporting Workbench was limited to 1 cardio- oncologist/amyloid specialist to mitigate possible performance issues, as this configuration is not designed to handle large queries.

**Results**

The Clarity report provided the most comprehensive and actionable database with regard to the patient yield, associated diagnoses identified within the EHR, and inclusion of billing transaction data (Figure 1). Of 45,051 patients with HF identified in the Epic EHR system, 4006 (8.9%) in the Clarity report satisfied at least 1 wild-type ATTR-CM phenotype combination criterion. Across data sources in the Clarity report, the majority of patients satisfying these criteria were ≥70 years of age (65%), male (53%), and White (76%).

In the CDS report, the silent alert was triggered 1584 times for 368 individual patients over a 48-day period; the operational Reporting Workbench report included 97 individual patients over a 48-day period for 1 cardiologist specializing in amyloidosis. The SlicerDicer reporting tool identified 11,646 patients who satisfied the phenotype combination criterion over a 3-year period, but the yield included duplicate patients and the patient information was not actionable.

In the Clarity report, across all data sources, of the 9 phenotypes associated with wild-type ATTR-CM included in this analysis, cardiomegaly (75.0%) and osteoarthritis (74.6%) identified the highest proportions of patients, and carpal tunnel syndrome (24.5%) and pleurisy (33.0%) identified the lowest (Figure 2A). Of the 20 phenotype combinations tested, carpal tunnel syndrome (25.1%) and atrial fibrillation + heart block + cardiomegaly + osteoarthritis (23.9%) identified the highest proportions of patients for follow-up evaluation, and atrial fibrillation + cardiomegaly + joint disorder + osteoarthritis + pleurisy (6.4%) and atrial fibrillation or cardiomegaly + carpal tunnel syndrome (8.8% each) identified the lowest (Figure 2B). The combination of carpal tunnel syndrome and atrial fibrillation was one of the more restrictive phenotypes, but still identified 352 patients at high risk for underlying and undiagnosed cardiac amyloidosis.

**Limitations**

Implementation of the phenotypes and phenotype combinations using various EHR configurations identified patients at increased risk for ATTR-CM in our health system based on prior work. However, our approach cannot be considered definitive for the diagnosis of wild-type ATTR-CM. Rather, it should be employed as a starting point for identifying at-risk individuals for further assessment with imaging and other diagnostic modalities. Further research will be needed to validate whether these EHR configurations result in increased diagnosis of wild-type ATTR-CM in patients in the clinical practice setting.

**Discussion**

Previously recognized as an untreatable disease and associated with very poor outcomes, wild-type ATTR-CM is currently treatable with the transthyretin kinetic stabilizer tafamidis.7 Moreover, advances in imaging techniques, including repurposed bone scintigraphy, speckle-tracking echocardiography, and cardiac magnetic resonance, have offered the potential for non-invasive diagnosis of ATTR-CM earlier in the disease course.5 However, despite these therapeutic and diagnostic improvements, patients with this life-threatening disease continue to be underdiagnosed, due at least in part to a lack of awareness of the clinical clues that should prompt screening of at-risk patients.

To help improve identification of patients at risk for ATTR-CM, we used real-world data from a large academic medical center and affiliated hospitals to implement 9 discrete phenotypes and 20 phenotype combinations associated with wild-type ATTR-CM, which we adapted from a previously developed ML model for screening and identification of wild-type ATTR-CM in patients with HF.9 We successfully employed 2 EHR configurations (CDS and reporting tools) to identify patients at risk for this rare disease. Although all of the functional EHR configurations we tested proved to be capable of implementing these phenotypes and phenotype combinations, the reporting tool Clarity is expected to be the most complete and actionable option for initial implementation.
The type of EHR implementation considered optimal may vary from location to location, but the Clarity report had a number of strengths, giving it a clear advantage in our experience. The Clarity report is comprehensive, easily manipulated, and provides granular detail for further action and patient evaluation. For an initial implementation strategy, it gives a complete overview of a health system's at-risk population. In our study, the Clarity report identified 4006 patients with at least 1

![Figure 2. Proportion of patients identified in the Clarity report by (a) phenotype and (b) phenotype combination associated with wild-type ATTR-CM. Abbreviations: Afib, atrial fibrillation; ATTR-CM, transthyretin amyloid cardiomyopathy; CKD, chronic kidney disease; OA, osteoarthrosis.](image-url)

| Category                                      | No. of patients identified | Patients, % |
|-----------------------------------------------|----------------------------|-------------|
| Carbohydrate-related phenotypes               |                            |             |
| Atrial fibrillation/flutter                   | 2667                       | 58.9        |
| Cardiomegaly                                  | 3395                       | 75.0        |
| Heart block                                   | 2664                       | 58.9        |
| Carpal tunnel syndrome                        | 1107                       | 24.5        |
| Chronic kidney disease                        | 2596                       | 57.4        |
| Joint disorder                                | 2142                       | 47.3        |
| Osteoarthrosis                                | 3378                       | 74.6        |
| Soft tissue disease                           | 2159                       | 47.7        |
| Pleurisy or pleural effusion                  | 1494                       | 33.0        |

| Non-carbohydrate-related phenotypes           | No. of patients identified | Patients, % |
|-----------------------------------------------|----------------------------|-------------|
| Afib + carpal tunnel syndrome                 | 352                        | 8.8         |
| Afib + heart block + cardiomegaly + OA        | 958                        | 23.9        |
| Afib + heart block + cardiomegaly + CKD       | 582                        | 14.5        |
| Afib + heart block + cardiomegaly + CKD + OA  | 372                        | 9.3         |
| Afib + heart block + cardiomegaly + OA + CKD  | 664                        | 16.6        |
| Afib + heart block + cardiomegaly + OA + CKD  | 257                        | 6.4         |
| Afib + heart block + cardiomegaly + OA + CKD  | 390                        | 9.7         |
| Afib + heart block + cardiomegaly + OA + CKD  | 257                        | 8.8         |
| Afib + heart block + cardiomegaly + OA + CKD  | 357                        | 10.2        |
| Afib + heart block + cardiomegaly + OA + CKD  | 407                        | 8.9         |
| Afib + heart block + cardiomegaly + OA + CKD  | 815                        | 15.1        |
| Afib + heart block + cardiomegaly + OA + CKD  | 604                        | 20.3        |
| Afib + heart block + cardiomegaly + OA + CKD  | 453                        | 15.1        |
| Afib + heart block + cardiomegaly + OA + CKD  | 786                        | 11.3        |
| Afib + heart block + cardiomegaly + OA + CKD  | 484                        | 19.6        |
| Afib + heart block + cardiomegaly + OA + CKD  | 829                        | 12.1        |
| Afib + heart block + cardiomegaly + OA + CKD  | 391                        | 20.7        |
| Afib + heart block + cardiomegaly + OA + CKD  | 1006                       | 9.0         |
| Afib + heart block + cardiomegaly + OA + CKD  | 360                        | 25.1        |
ATTR-CM-related feature combination within the EHR over approximately 18 months, based on 4 data sources, including billing transactions. Although it may initially be more difficult to build, the upfront cost was outweighed by its overall usefulness and flexibility, including its ability to tap multiple data sources. Importantly, however, while billing transaction data identified additional, potentially at-risk patients in our study, the practical utilization of such data may not apply in an organic clinical setting. Acquisition of billing data can be challenging due to health system access restrictions, and clinicians may not intuitively recognize its clinical value.

EHR reports such as Reporting Workbench may also be effective tools to start identifying patients at potential risk for wild-type ATTR-CM, offering several benefits, such as accessibility to clinicians and convenience in building. The number of patients yielded in such reports will be lower, which may be more manageable for staff in the clinical practice setting. However, EHR reports can have system performance limitations and frequent time-outs based on query duration and size. Based on our observations, depending on the provider’s health information technology capabilities, Reporting Workbench may be a useful tool to pilot the search in the EHR of a single clinic or provider, as the tool provides output that can be reviewed by allocated staff in a timely fashion. The data warehouse tool (SlicerDicer) delivered an initial estimation of the number of patients who met the stipulated criteria within our health system and were therefore potentially at risk for wild-type ATTR-CM, but it cannot be used alone due to the lack of patient identifiers. In addition, the SlicerDicer tool cannot recognize duplicate patients identified through different combinations and does not yield actionable patient information.

Alternatively, the CDS offered the advantage of identifying patients in real time, which provides an alternative method to keeping the patient list more manageable for initial implementation. However, because the CDS only fires on an individual patient encounter, it would require a substantial amount of time to identify all patients at risk within a health system. A potential solution would be to implement both the analytical Clarity report, to initially identify patients within the health system, and the CDS, to continue identifying patients in real time.

The CDS presents other unique considerations that are worth addressing. In previous alert systems, “alert fatigue” has been shown to result in high override alert rates, limiting the effectiveness of the approach. Additionally, healthcare providers may not be familiar with amyloidosis disease or its evaluation, and the CDS would require clear and detailed guidance on disease management, including referral to an amyloid specialist and/or concurrent alerts sent to colleagues with expertise in cardiac amyloidosis who could provide further evaluation. This is particularly helpful for rare diseases such as ATTR-CM, which often require a multidisciplinary healthcare approach. While these algorithms have identified wild-type ATTR-CM versus non-amyloid HF with high accuracy (ie, 74%) in an administrative data cohort, patients will still require further evaluation with cardiovascular imaging, and potentially biopsy, to confirm the diagnosis. Classic findings on echocardiogram (eg, reduced annular velocities [the 5-5-5 sign]; reduced global longitudinal strain, with or without apical sparing; and left ventricular hypertrophy) or cardiac MRI (eg, abnormalities in T1 and T2 mapping; increased extracellular volume; and late gadolinium enhancement) can be seen in many, but not all, patients with ATTR-CM. However, bone scintigraphy is the only currently available imaging modality that can be used to definitively diagnose wild-type ATTR-CM, outside of endomyocardial biopsy. Incorporation of cardiovascular imaging findings may be considered in future algorithms to identify patients at risk for wild-type ATTR-CM, but the elegance of the current approach lies in its simplicity and ability to be applied widely to patients even if they have not yet undergone advanced cardiovascular imaging.

Conclusions
Our research suggests that high-performing predictive phenotypes and phenotype combinations adapted from an ML algorithm can be implemented in a health system’s EHR, offering a systematic approach to timely identification of patients at risk for wild-type ATTR-CM who may otherwise remain unrecognized. Furthermore, it provides a practical example of the systematic application of a CDS tool to a population data-set to facilitate identification of at-risk patients for a rare disease. Additional research is needed to further validate the output of the data sources and inform CDS for at-risk patients with this underdiagnosed, life-threatening disease, and to establish the framework of clinical care pathways for these patients following their identification.

Implications
The preliminary results obtained at our academic medical center suggest the feasibility of implementing high-performing phenotypes and phenotype combinations with 1 or more EHR configuration options to identify patients at risk of wild-type ATTR-CM who could benefit from further evaluation (eg, scintigraphy), offering potential opportunities for successful use within other healthcare system databases or at the point of care.

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REFERENCES

1. Rapezzi C, Quarta CC, Riva L, et al. Transthyretin-related amyloidoses and the heart: a clinical overview. *Nat Rev Cardiol*. 2010;7:398-408.

2. Bonderman D, Polzl G, Ablaiser K, et al. Diagnosis and treatment of cardiac amyloidosis: an interdisciplinary consensus statement. *Wien Klin Wochenschr*. 2020;132:742-761.

3. Lindmark K, Pilebo B, Sundström T, Lindqvist P. Prevalence of wild type transthyretin cardiac amyloidosis in a heart failure clinic. *ESC Heart Fail*. 2021;8:745-749.

4. Hahn VS, Yanek LR, Vaishnav J, et al. Endomyocardial biopsy characterization of heart failure with preserved ejection fraction and prevalence of cardiac amyloidosis. *JACC Heart Fail*. 2020;8:712-724.

5. Witteles RM, Bokhari S, Damy T, et al. Screening for transthyretin amyloid cardiomyopathy in everyday practice. *JACC Heart Fail*. 2019;7:709-716.

6. Bishop E, Brown EE, Fajardo J, Barouch LA, Judge DP, Hulshaka MK. Seven factors predict a delayed diagnosis of cardiac amyloidosis. *Amyloid*. 2018;25:174-179.

7. Maurer MS, Schwartz JH, Gundapaneni B, et al. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. *Engl J Med*. 2018;379:1007-1016.

8. Fosbøl EL, Raehal R, Leicht BP, et al. Association of carpal tunnel syndrome with amyloidosis, heart failure, and adverse cardiovascular outcomes. *J Am Coll Cardiol*. 2019;74:15-23.

9. Huda A, Castaño A, Niyogi A, et al. A machine learning model for identifying patients at risk for wild-type transthyretin amyloid cardiomyopathy. *Nat Commun*. 2021;12:2725.

10. Heitner S, Elman MR, Masri A, et al. Performance evaluation of a machine learning model for systematic identification of wild-type transthyretin amyloid cardiomyopathy at two academic medical centers. *J Card Fail*. 2020;26:S38.

11. Huda A, Heitner S, Calambur V, Bruno M, Schumacher J, Emir B. A machine learning framework for predicting risk of wild-type transthyretin amyloid cardiomyopathy. Paper presented at: XVIth International Symposium on Amyloidosis; September 14-18, 2020; Virtual event.

12. Denny JC, Ritchie MD, Basford MA, et al. PhEWS: demonstrating the feasibility of a phenome-wide scan to discover gene-disease associations. *Bioinformatics*. 2010;26:1205-1210.

13. van der Sij H, Aarts J, Vulto A, Berg M. Overriding of drug safety alerts in computerized physician order entry. *J Am Med Inform Assoc*. 2006;13:138-147.

14. Nanji KC, Slight SP, Seger DL, et al. Overrides of medication-related clinical decision support alerts in outpatients. *J Am Med Inform Assoc*. 2014;21:487-491.

15. Gerza M, Adams D, Ando Y, et al. Avoiding misdiagnosis: expert consensus recommendations for the suspicion and diagnosis of transthyretin amyloidosis for the general practitioner. *BMC Fam Pract*. 2020;21:198.

16. Nakov R, Suhr OB, Janito G, et al. Recommendations for the diagnosis and management of transthyretin amyloidosis with gastrointestinal manifestations. *Eur J Gastroenterol Hepatol*. 2021;33:613-622.

17. Hafeez AS, Bavry AA. Diagnosis of transthyretin amyloid cardiomyopathy. *Cardiol Ther*. 2020;9:85-95.

18. Itzhaki Ben Zadok O, Kornowski R. Cardiac care of patients with cardiac amyloidosis. *Acta Haematol*. 2020;143:343-351.

19. Dang D, Fournier P, Carlou E, et al. Gateway and journey of patients with cardiac amyloidosis. *ESC Heart Fail*. 2020;7:2418-2430.

20. Gillmore JD, Maurer MS, Falk RH, et al. Nonbiopsy diagnosis of cardiac transthyretin amyloidosis. *Circulation*. 2016;133:2403-2412.

21. Kyrouac D, Schiffer W, Lennep B, et al. Echocardiographic and clinical predictors of cardiac amyloidosis: limitations of apical sparing. *ESC Heart Fail*. 2022;9:385-397.