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Research Article

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Age-adjusted baseline D-dimer predicts thrombotic events during readmission in anticoagulated patients with non-valvular atrial fibrillation

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Abstract

Background: Patients with non-valvular atrial fibrillation (NVAF) remain at substantial risk of thrombotic and bleeding events despite oral anticoagulation, and readmission is a common and costly consequence. D-dimer reflects persistent coagulation and fibrinolysis activation and has been associated with adverse outcomes in atrial fibrillation, but whether a single baseline measurement can predict events during readmission remains unclear.

Methods: We retrospectively studied 1,108 anticoagulated patients with NVAF who had multiple hospitalisations at our institution between 2018 and 2022. Patients were stratified by baseline D-dimer according to an age-adjusted cut-off. The primary endpoint was a composite of thrombotic events, major bleeding and death during readmission, adjudicated by a hierarchical first-event rule. Multivariable Cox regression was performed in the 899 patients with complete CHA_2DS_2-VASc and HAS-BLED scores. Sensitivity analyses included propensity score matching (230 pairs) and a competing-risk model and a 30-day landmark analysis. The incremental value of the age-adjusted D-dimer cut-off beyond CHA_2DS_2-VASc was assessed by the C-statistic.

Results: The abnormal-D-dimer group had a higher incidence of the composite endpoint (24.0% vs 9.6%, P<0.001) and of thrombotic events (19.7% vs 8.2%, P<0.001). Abnormal D-dimer independently predicted the composite endpoint (adjusted HR 1.64, 95% CI 1.09–2.47) and thrombotic events (adjusted HR 2.02, 95% CI 1.30–3.15), but not major bleeding (HR 1.46, 95% CI 0.44–4.90) or death during readmission (HR 1.73, 95% CI 0.54–5.52). Sensitivity analyses were consistent for the composite and thrombotic endpoints, whereas bleeding and death events were too few for reliable estimates. Adding D-dimer to CHA_2DS_2-VASc improved discrimination (ΔC=0.034, 95% CI 0.006–0.076) and reclassification (24-month NRI=43.8%; IDI=0.025).

Conclusions: In anticoagulated patients with NVAF, a baseline D-dimer above the age-adjusted cut-off independently predicts thrombotic events during subsequent readmission and provides incremental predictive information beyond CHA_2DS_2-VASc.

Clinical trial number: not applicable.

Keywords: non-valvular atrial fibrillation; D-dimer; oral anticoagulation; hospital readmission; thrombotic events; risk stratification

1. Introduction

Atrial fibrillation (AF), and non-valvular AF (NVAF) in particular, affects millions of people worldwide. Oral anticoagulation (OAC) substantially reduces the risk of stroke [3,4], but a residual thrombotic risk persists [1,2], and readmission is a particularly important manifestation of this residual risk. The CHA_2DS_2-VASc score is the standard risk stratification tool, but its discrimination is limited (C-statistic approximately 0.6) and it does not reflect an individual's prothrombotic state [5].

D-D-dimer reflects persistent coagulation activation and predicts adverse outcomes in cardiovascular disease [14]. In anticoagulated AF cohorts, elevated D-dimer has been associated with stroke and mortality [15,16]; however, previous studies used fixed or quartile-based thresholds, which lack specificity in older patients. In patients with AF, elevated D-dimer has additionally been associated with left atrial thrombus and severe spontaneous echo contrast

[12,13]. An age-adjusted D-dimer cut-off has been validated for ruling out venous thromboembolism (VTE), but its prognostic value in NVAF remains to be tested.

AF is a leading cause of cardiovascular hospitalisation worldwide, and approximately 10% of patients are readmitted within 30 days of an index AF admission [7–9]. In biomarker studies, however, readmission remains a rarely studied risk window. No study has yet examined whether a single baseline D-dimer measurement at the index admission predicts adverse events during readmission in anticoagulated patients with NVAF.

We therefore retrospectively analysed 1,108 anticoagulated patients with NVAF who had multiple hospitalisations at our institution between 2018 and 2022, to determine whether a D-dimer level above the age-adjusted cut-off independently predicts adverse events during readmission and provides incremental value beyond the CHA_2DS_2-VASc score.

2. Methods

2.1 Study design and population

We consecutively screened patients admitted to our institution with atrial fibrillation (AF) between 1 January 2018 and 31 December 2022. Inclusion criteria were: (1) age ≥18 years; (2) AF documented by electrocardiography or 24-h Holter monitoring; (3) regular oral anticoagulant therapy (rivaroxaban, dabigatran or warfarin); (4) D-dimer measured on admission; and (5) at least two documented hospitalisations during follow-up. Exclusion criteria were: (1) valvular heart disease (moderate-to-severe mitral stenosis or a mechanical prosthetic heart valve); (2) severe anaemia at baseline (Hb<60 g/L); (3) active malignancy; (4) severe hepatic impairment (Child–Pugh class C) or end-stage renal disease (eGFR<15 mL/min/1.73 m^2); and (5) severely incomplete data. The patient selection process is shown in Figure 1.

The study was approved by the institutional ethics committee of our hospital (approval no. WAGHMEC-KT-2021015). Given the retrospective and de-identified nature of the study, the requirement for informed consent was waived.

2.2 D-dimer measurement and definition of exposure

Plasma D-dimer was measured with an ACL-TOP 700 analyser (Werfen, USA) using HemosIL HS 500 reagent, and results were reported in fibrinogen equivalent units (FEU, μg/L).

We used an age-adjusted cut-off: <50 years, 500 μg/L; ≥50 years, age × 10 μg/L [21,22]. Patients were classified into an "abnormal" or "normal" group according to their D-dimer level at the index admission (baseline).

2.3 Endpoints

The index admission served as time zero, and follow-up continued until the first event during readmission. The primary endpoint was a composite of: (i) thromboembolism (ischaemic stroke, myocardial infarction, cardiac thrombus, pulmonary embolism, deep vein thrombosis or systemic embolism); (ii) major bleeding (intracranial or gastrointestinal bleeding); and (iii) death during readmission. The three individual components were analysed separately as secondary endpoints. Events occurring during the index admission were not counted. When more than one endpoint occurred, a hierarchical first-event rule was applied (death > major bleeding > thromboembolism).

2.4 Statistical analysis

Continuous variables are presented as mean ± SD or median (IQR) and compared using Student's t-test or Mann–Whitney U test. Categorical variables are reported as counts (%) and compared using χ^2 or Fisher's exact test.

The primary analysis used multivariable Cox proportional hazards regression to estimate HRs and 95% CIs for the composite endpoint and thrombotic events, adjusted for age, sex, CHA_2DS_2-VASc and HAS-BLED scores [6], and comorbidities (hypertension, chronic heart failure, myocardial infarction, stroke, coronary artery disease, and renal or hepatic dysfunction); the full models are shown in Supplementary Table S2.

Three sensitivity analyses were performed: (1) a 30-day landmark analysis excluding early events; (2) 1:1 propensity score matching (caliper 0.2), yielding 230 matched pairs; and (3) a competing-risk model treating death as a competing event (Fine–Gray regression).

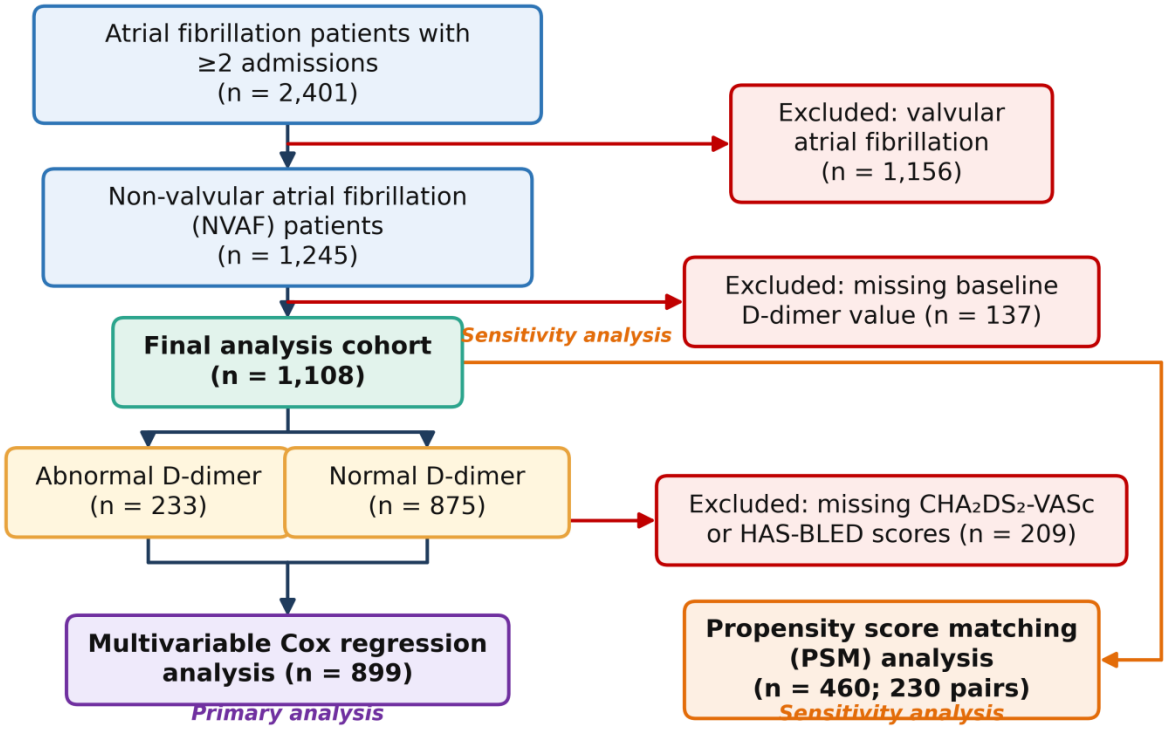
Incremental predictive value of D-dimer beyond CHA_2DS_2-VASc was assessed by C-statistic (1,000 bootstrap samples), NRI (24 months), and IDI.

All tests were two-sided, with $P<0.05$ considered significant. Statistical analyses were performed with Python 3.13 using the lifelines 0.29 library.

3. Results

3.1 Patient characteristics

A total of 1,108 patients with NVAF were ultimately included: 875 in the normal group and 233 in the abnormal group (Figure 1). Of these, 899 had complete CHA_2DS_2-VASc and HAS-BLED scores and were included in the multivariable regression analysis; after propensity score matching there were 460 patients (230 pairs). Baseline characteristics across the 13 matching covariates were well balanced (all SMD<0.1) (Table 1); renal and hepatic dysfunction, which were not used as matching covariates, remained residually imbalanced.



NVAF = non-valvular atrial fibrillation; PSM = propensity score matching; CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥75 years, diabetes, stroke/TIA, vascular disease, age 65–74 years, sex category.

Figure 1. Flowchart of patient selection.

Table 1. Baseline characteristics of patients with NVAF before and after propensity score matching

Variable	Before PSM				After PSM			
	Normal (n=875)	Abnormal (n=233)	SMD	P	Normal (n=230)	Abnormal (n=230)	SMD	P
Age (years)	64.5 ± 11.0	66.8 ± 11.9	0.202	0.003	67.0 ± 12.0	66.6 ± 11.8	0.034	0.623
BMI	25.2 ± 3.6	24.8 ± 4.0	0.108	0.164	24.9 ± 3.4	24.9 ± 3.7	0.009	0.989
CHA_2DS_2-VASc score	3.0 ± 1.7	3.6 ± 1.9	0.302	<0.001	3.5 ± 1.8	3.5 ± 1.9	0.012	0.872
HAS-BLED score	1.8 ± 1.1	2.0 ± 1.2	0.176	0.018	1.9 ± 1.1	2.0 ± 1.2	0.022	0.793
Age >50 years	781 (89.3%)	209 (89.7%)	0.014	0.846	209 (90.9%)	206 (89.6%)	0.044	0.638
Female	310	85 (36.5%)	0.022	0.766	89	84 (36.5%)	0.045	0.630

	(35.4%)				(38.7%)			
Diabetes	193 (22.1%)	55 (23.6%)	0.037	0.614	51 (22.2%)	54 (23.5%)	0.031	0.739
Hypertension	557 (63.7%)	141 (60.5%)	0.065	0.377	129 (56.1%)	140 (60.9%)	0.097	0.298
Chronic heart failure	67 (7.7%)	60 (25.8%)	0.499	<0.001	58 (25.2%)	57 (24.8%)	0.010	0.914
Prior thromboembolism	287 (32.8%)	66 (28.3%)	0.097	0.193	68 (29.6%)	66 (28.7%)	0.019	0.837
Coronary artery disease	692 (79.1%)	168 (72.1%)	0.163	0.023	165 (71.7%)	166 (72.2%)	0.010	0.917
Current smoking	330 (37.7%)	88 (37.8%)	0.001	0.988	83 (36.1%)	87 (37.8%)	0.036	0.699
Current drinking	157 (17.9%)	34 (14.6%)	0.091	0.229	38 (16.5%)	33 (14.3%)	0.060	0.519
Hepatic dysfunction*	12 (1.4%)	13 (5.6%)	0.231	<0.001	4 (1.7%)	12 (5.2%)	0.190	0.072
Renal dysfunction*	70 (8.0%)	52 (22.3%)	0.407	<0.001	26 (11.3%)	49 (21.3%)	0.273	0.004
Stroke history*	259 (29.6%)	52 (22.3%)	0.166	0.028	60 (26.1%)	52 (22.6%)	0.081	0.385
Myocardial infarction history*	44 (5.0%)	21 (9.0%)	0.156	0.021	13 (5.7%)	21 (9.1%)	0.133	0.154

Note: Continuous variables are shown as mean ± SD; categorical variables as n (%). SMD, standardised mean difference. * Not included in the matching procedure; residual imbalance was assessed as a reference covariate.

3.2 Clinical events and survival analysis

Median follow-up was 8.6 months (IQR 2.6–22.1). During follow-up, the abnormal-D-dimer group had significantly higher incidences of the composite endpoint (24.0% vs 9.6%, P<0.001), thrombotic events (19.7% vs 8.2%, P<0.001), major bleeding (3.4% vs 0.9%, P=0.003) and death during readmission (3.9% vs 0.9%, P<0.001) (Table 2). Kaplan–Meier curves showed significantly lower event-free survival in the abnormal group (log-rank P<0.001 for both endpoints) (Figure 2).

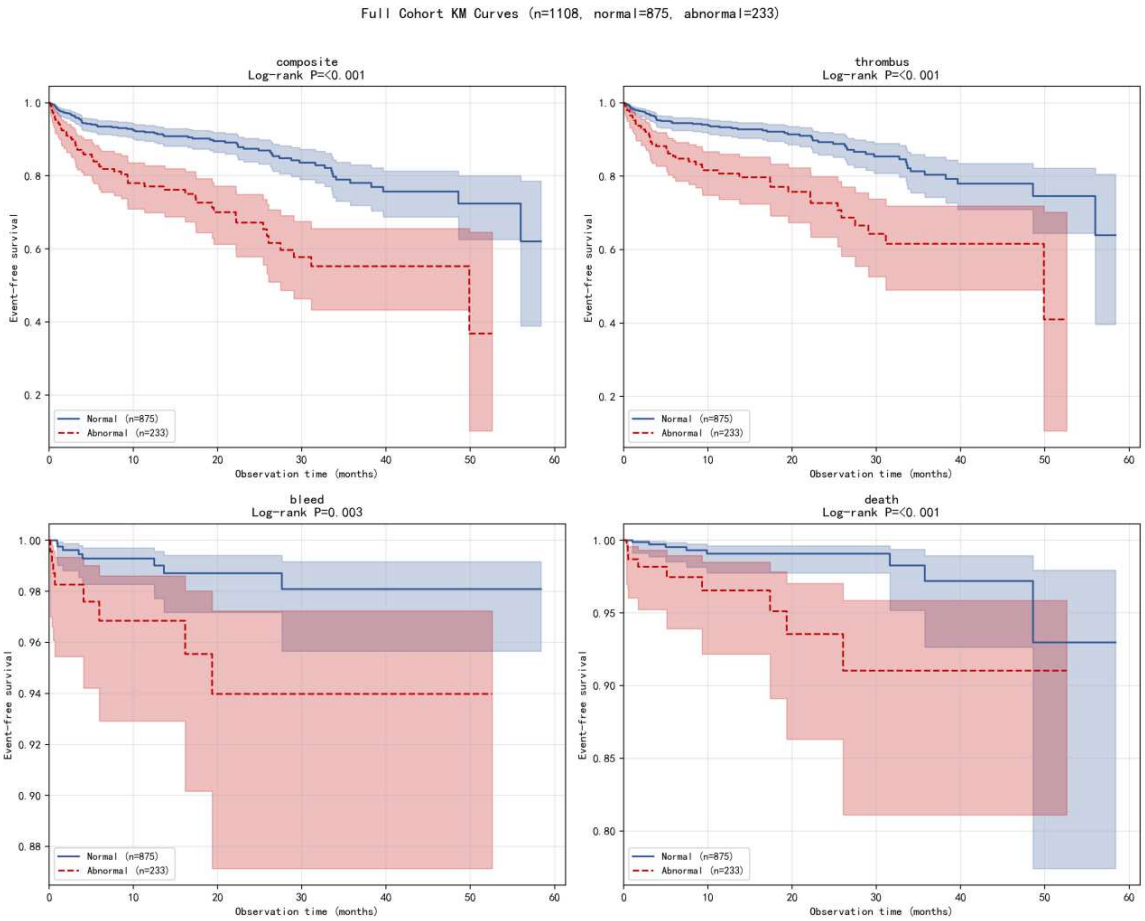


Figure 2. Kaplan–Meier event-free survival curves for the full cohort.

Table 2. Event rates for clinical endpoints and Cox regression analysis in the full cohort

Endpoint	Events (%)			P (log-rank)	Univariable HR (95% CI) (n=1,108)	P	Multivariable HR (95% CI) (n=899)	P
	Full cohort (n=1,108)	Abnormal D-dimer (n=233)	Normal D-dimer (n=875)					
Composite endpoint	140 (12.6%)	56 (24.0%)	84 (9.6%)	<0.001	2.82 (2.01–3.96)	<0.001	1.64 (1.09–2.47)	0.017
Thrombotic events	118 (10.7%)	46 (19.7%)	72 (8.2%)	<0.001	2.71 (1.87–3.93)	<0.001	2.02 (1.30–3.15)	0.002
Major bleeding	16 (1.4%)	8 (3.4%)	8 (0.9%)	0.003	3.92 (1.47–10.46)	0.006	1.46 (0.44–4.90)	0.538
Death during readmission	17 (1.5%)	9 (3.9%)	8 (0.9%)	<0.001	4.57 (1.76–11.85)	0.002	1.73 (0.54–5.52)	0.352

Note: HR, hazard ratio; CI, confidence interval.

3.3 Cox regression analysis

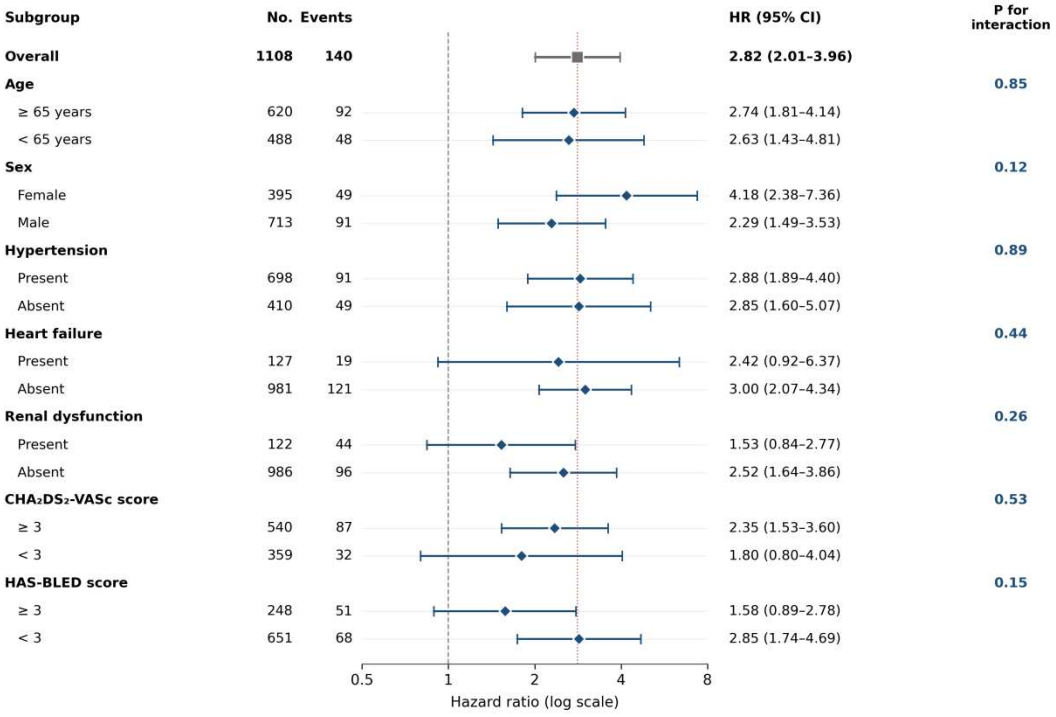
Multivariable Cox regression in the 899 patients showed that abnormal D-dimer was an independent predictor of the composite endpoint (adjusted HR 1.64, 95% CI 1.09–2.47, P=0.017) and of thrombotic events (adjusted HR 2.02, 95% CI 1.30–3.15, P=0.002), independent of age, sex, CHA_2DS_2-VASc score, HAS-BLED score and comorbidities (Table 2, Supplementary Table S2). There was no statistically significant association with major bleeding (adjusted HR 1.46, 95% CI 0.44–4.90) or death during readmission (adjusted HR 1.73, 95% CI 0.54–5.52). Renal dysfunction was the strongest independent covariate for the composite endpoint (adjusted HR 2.85, 95% CI 1.82–4.46, P<0.001).

3.4 Subgroup analysis, sensitivity analyses and incremental predictive value

The predictive effect of abnormal D-dimer on the composite endpoint was consistent across subgroups, including age, sex, hypertension status, chronic heart failure, renal dysfunction, and CHA_2DS_2-VASc and HAS-BLED strata; no interaction term reached statistical significance (all P for interaction >0.05) (Figure 3).

In the PSM cohort, the hazard ratio for the composite endpoint was 2.69 (95% CI 1.67–4.35, P<0.001), and the estimate attenuated only slightly after additional adjustment for renal and hepatic dysfunction (adjusted HR 2.30, 95% CI 1.41–3.75, P<0.001). The competing-risk analysis with death as a competing event gave consistent results (subdistribution HR 2.60, 95% CI 1.77–3.80, P<0.001). For major bleeding, the crude associations observed in the univariable and sensitivity analyses (univariable HR 3.92; competing-risk SHR 2.93, 95% CI 1.02–8.45, P=0.046; landmark HR 2.99, 95% CI 1.04–8.61, P=0.043) were not reproduced in the multivariable model (adjusted HR 1.46, 95% CI 0.44–4.90) (Table 2, Supplementary Table S1, Supplementary Table S2).

Adding abnormal D-dimer to a model containing only the CHA_2DS_2-VASc score improved discrimination for the composite endpoint (C-statistic 0.649 vs 0.616; ΔC=0.034, 95% CI 0.006–0.076; likelihood ratio test P<0.001). Reclassification at 24 months also improved (category-free NRI 43.8%, 95% CI 18.3%–70.2%; IDI 0.025, 95% CI 0.004–0.067).



Hazard ratios were derived from univariable Cox proportional-hazards models for the composite endpoint (death, bleeding, or thrombotic events after readmission), comparing abnormal with normal baseline D-dimer. The red dotted line indicates the overall hazard ratio. P for interaction was obtained from Cox models including the corresponding product term. CHA_2DS_2-VASc and HAS-BLED score subgroups were restricted to the 899 patients with available scores.

Figure 3. Forest plot of the subgroup analysis. The red dashed line indicates the overall univariable hazard ratio (HR=2.82, 95% CI 2.01–3.96).

4. Discussion

4.1 Principal findings

In this retrospective cohort of 1,108 anticoagulated patients with NVAF and at least two hospitalisations, a baseline D-dimer level above the age-adjusted cut-off identified patients at substantially higher risk of adverse events during readmission. The abnormal-D-dimer group had a more than twofold higher crude incidence of the composite endpoint (24.0% vs 9.6%, P<0.001) and of thrombotic events (19.7% vs 8.2%, P<0.001). After adjustment for age, sex, CHA_2DS_2-VASc and HAS-BLED scores and comorbidities in the 899 patients with complete scoring, abnormal D-dimer remained an independent predictor of the composite endpoint (adjusted HR 1.64, 95% CI 1.09–2.47, P=0.017) and, more strongly, of thrombotic events (adjusted HR 2.02, 95% CI 1.30–3.15, P=0.002). The association was robust across three sensitivity analyses—propensity score matching (HR 2.69, 95% CI 1.67–4.35), competing-risk analysis with death as a competing event (subdistribution HR 2.60, 95% CI 1.77–3.80) and a 30-day landmark analysis (HR 2.54, 95% CI 1.78–3.63)—and was consistent across all prespecified subgroups, with no significant interaction for age, sex, hypertension, chronic heart failure, renal dysfunction or either clinical risk score (all P for interaction >0.05).

The signal was, however, endpoint-specific. In the fully adjusted model, abnormal D-dimer was not associated with major bleeding (adjusted HR 1.46, 95% CI 0.44–4.90, P=0.538) or with death during readmission (adjusted HR 1.73, 95% CI 0.54–5.52, P=0.352), despite significantly higher crude rates of both in the abnormal group. Adding D-dimer to a model containing only CHA_2DS_2-VASc improved discrimination for the composite endpoint (C-statistic 0.649 vs 0.616; ΔC=0.034, 95% CI 0.006–0.076) and reclassification at 24 months (NRI 43.8%, 95% CI 18.3%–70.2%; IDI 0.025, 95% CI 0.004–0.067).

4.2 Comparison with previous studies

Our findings extend a consistent body of evidence linking D-dimer to thromboembolic risk in AF. Sadanaga and colleagues were among the first to show, in 269 warfarin-treated patients with AF, that an elevated D-dimer predicted subsequent thromboembolic events during anticoagulation [14]. That observation has since been reproduced in large randomised-trial

substudies: in ARISTOTLE, higher D-dimer was associated with stroke or systemic embolism, death and major bleeding, and improved the C-index of the $CHADS_2$ score [15]; in RE-LY, D-dimer formed part of a multimarker panel associated with stroke and death [16]; and in ENGAGE AF-TIMI 48, serial biomarker assessment showed that D-dimer trajectories tracked residual risk [17]. In the elderly ANAFIE population, higher D-dimer was likewise associated with cardiovascular events and death, with different patterns in DOAC- and warfarin-treated patients [18]. A recent multi-biomarker study in 3,817 patients with AF confirmed D-dimer as one of five biomarkers that independently predicted cardiovascular death, stroke, myocardial infarction and systemic embolism, and improved prediction beyond clinical risk scores [25].

Our study differs from these in three respects that we consider clinically important. First, we used an age-adjusted cut-off (500 μg/L below 50 years; age × 10 μg/L at or above 50 years), derived from the diagnostic literature on venous thromboembolism [21,22], rather than the fixed or quartile-based thresholds used in most prognostic studies. Because D-dimer rises physiologically with age, a fixed threshold classifies a disproportionate number of older patients as abnormal; an age-adjusted threshold therefore has better specificity in exactly the population that dominates NVAF cohorts. Second, our outcome was anchored to the readmission period rather than to an unrestricted follow-up window. Readmission is a common and costly consequence of AF hospitalisation—approximately one in ten patients is readmitted within 30 days [7], and readmission independently predicts long-term mortality [8]—yet it has rarely been used as the risk window in biomarker studies. Third, we focused on patients who were already anticoagulated at baseline, a group in which residual thrombotic risk is by definition the clinically relevant question, and we deliberately analysed bleeding and death as separate endpoints rather than collapsing them into the composite.

The endpoint-specificity we observed is also consistent with the literature. In our cohort, abnormal D-dimer was associated with thrombosis but not, after adjustment, with major bleeding or death. In ARISTOTLE, D-dimer was related to both thrombotic and bleeding events [15], and a recent narrative review concluded that D-dimer is a component of the ABC-bleeding score and is independently associated with bleeding [26]. Our bleeding result should be read against a much smaller number of events (16 major bleeds overall, 8 in the abnormal group) and a consequently wide confidence interval (0.44–4.90) that does not exclude a clinically relevant

association. The apparent discrepancy is therefore more likely to reflect limited statistical power than a genuine biological difference.

4.3 Potential mechanisms

D-dimer is the terminal degradation product of cross-linked fibrin and therefore integrates two processes: ongoing thrombin generation with fibrin formation, and secondary fibrinolysis. In AF, this reflects the interplay between atrial endothelial dysfunction, inflammation and a prothrombotic atrial substrate—an association documented in patients with chronic AF even during warfarin therapy [10,11]. A baseline D-dimer above the age-adjusted cut-off can thus be interpreted as an index of a persistently activated coagulation system that continues to generate fibrin despite adequate anticoagulation, which is mechanistically coherent with the residual thrombotic risk seen in anticoagulated AF populations.

Two ancillary observations from our data support this interpretation. First, the effect of D-dimer was confined to thrombotic events; the point estimates for bleeding and death were directionally consistent but imprecise, as would be expected if D-dimer primarily marks thrombogenesis rather than a generalised frailty state. Second, and importantly, renal dysfunction—not D-dimer—was the strongest independent covariate for the composite endpoint (adjusted HR 2.85, 95% CI 1.82–4.46, P<0.001). This is relevant because D-dimer is cleared in part by the kidney, and elevated levels in renal impairment may partly reflect reduced clearance rather than increased thrombogenesis [23,24]. In our cohort, renal dysfunction was substantially more frequent in the abnormal-D-dimer group before matching (22.3% vs 8.0%), and it remained imbalanced after propensity score matching (21.3% vs 11.3%, SMD 0.273). When renal and hepatic dysfunction were added to the matched model, the hazard ratio for the composite endpoint attenuated from 2.69 to 2.30 but remained significant (95% CI 1.41–3.75, P<0.001). We therefore suggest that part, but not all, of the D-dimer signal is confounded by renal function, and that D-dimer should not be interpreted in isolation from renal status in this population.

4.4 Clinical implications

CHA_2DS_2-VASc is the standard tool for stroke risk stratification in AF, but its discrimination is modest (C-statistic approximately 0.6) and it captures static clinical variables rather than the

dynamic biological state of the patient [1,5]. Biomarker-based scores such as the ABC stroke and ABC-AF scores, which incorporate D-dimer and other biomarkers, have been developed to refine risk prediction beyond clinical variables [19,20]. Our results indicate that a single admission measurement of D-dimer, interpreted against an age-adjusted cut-off, adds prognostic information beyond CHA_2DS_2-VASc for thrombotic events in anticoagulated NVAF patients—an improvement in the C-statistic of 0.034 and an NRI of 43.8% at 24 months. Because D-dimer is inexpensive, widely available and already measured in most hospitalised patients, this would represent a low-cost addition to existing risk assessment rather than a new test.

Several caveats must accompany this suggestion. A ΔC of 0.034 is statistically significant but modest, and NRI values of this magnitude are sensitive to the choice of risk thresholds and require external validation before they can justify a change in management. We emphasise that our data do not support using D-dimer to withhold anticoagulation, nor to escalate anticoagulant intensity on the basis of D-dimer alone; the appropriate use of such a marker would be to flag patients who warrant closer post-discharge surveillance and structured follow-up—an approach supported by evidence that readmission after AF hospitalisation is common and associated with worse long-term survival [8,9]. Prospective studies with predefined D-dimer thresholds and standardised follow-up are required before this can be translated into practice.

4.5 Limitations

Our study has several limitations. First, its retrospective, single-centre design means that residual confounding cannot be excluded, and the findings require external validation in independent and more ethnically diverse cohorts. Second, D-dimer was measured once, at baseline; serial measurements might better capture the dynamic thrombotic state, and our data cannot address whether changes in D-dimer over time carry additional prognostic information. Third, although we used an age-adjusted cut-off, no D-dimer threshold has been prospectively validated for prognostic use in NVAF, and our exposure definition was therefore borrowed from the diagnostic venous thromboembolism literature [21,22]. Fourth, renal dysfunction was imbalanced between groups even after matching, and although the association persisted after adjustment, confounding by renal function cannot be fully excluded; the absence of routine

eGFR-adjusted D-dimer interpretation is a further limitation. Fifth, we could not fully account for the heterogeneity of anticoagulant regimens (rivaroxaban, dabigatran or warfarin).

5. Conclusions

In anticoagulated patients with NVAF, a baseline D-dimer above the age-adjusted cut-off independently predicts thrombotic events during subsequent readmission and provides incremental predictive value beyond the CHA_2DS_2-VASc score. No corresponding multivariable signal was observed for bleeding or death, and against a background of sparse events the specificity of D-dimer as a thrombotic marker remains unresolved and should be interpreted with caution. If confirmed prospectively, a single admission D-dimer measurement could serve as a practical, low-cost means of identifying patients who require intensified post-discharge surveillance.

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Declarations

Ethics approval and consent to participate

The study was approved by the Institutional Ethics Committee of Wuhan Asia General Hospital (WAGHMEC-KT-2021015) and was conducted in accordance with the Declaration of Helsinki. Because the study was retrospective and all data were de-identified before analysis, the institutional ethics committee waived the requirement for written informed consent. This manuscript does not report any information that could identify individual participants.

Consent for publication

Not applicable. This manuscript does not contain any form of individual data, and no consent for publication is required.

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available because they contain individual patient clinical information obtained under institutional ethics approval that does not permit public deposition. The de-identified dataset and analysis code are available from the corresponding author on reasonable request and with permission from the institutional ethics committee of Wuhan Asia General Hospital.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Litao Zhang and Xiaosu Wang conceived and designed the study. Jingdan Yu and Qichao Li performed data collection and endpoint adjudication. Xiaosu Wang performed the statistical analysis and wrote the first draft of the manuscript. Dan Zhang and Zheng Dai participated in the interpretation of results and critically revised the manuscript for important intellectual content. Xinsheng Yan and Xiaosu Wang (corresponding author) was responsible for project supervision and administrative support. All authors read and approved the final manuscript and agree to be accountable for all aspects of the work.

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Authors' information

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Abbreviations

ABC, age, biomarkers, clinical history; AF, atrial fibrillation; BMI, body mass index; CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischaemic attack, vascular disease, age 65–74 years, sex category; $CHADS_2$, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischaemic attack; CI, confidence interval; DOAC, direct oral anticoagulant; FEU, fibrinogen equivalent units; HAS-BLED, hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly, drugs/alcohol; HR, hazard ratio; IDI, integrated discrimination improvement; INR, international normalized ratio; IQR, interquartile range; NVAF, non-valvular atrial fibrillation; NRI, net reclassification improvement; OAC, oral

anticoagulation; PSM, propensity score matching; SD, standard deviation; SHR, subdistribution hazard ratio; SMD, standardised mean difference; VTE, venous thromboembolism.

Supplementary materials

Supplementary Table S1. Sensitivity analyses of the association between D-dimer level and clinical endpoints

Analysis method	Endpoint	N	Events	HR/SHR (95% CI)	P value
PSM-matched cohort (230 pairs, n=460)	Composite endpoint	460	80	2.69 (1.67–4.35)	<0.001
	Thrombotic events	460	61	3.57 (1.99–6.41)	<0.001
	Bleeding events	460	12	2.09 (0.63–6.93)	0.230
	Death during readmission	460	15	1.70 (0.60–4.77)	0.317
Competing-risk analysis (Fine–Gray SHR, death as competing event)	Thrombotic events	1,108	113	SHR=2.60 (1.77–3.80)	<0.001
	Bleeding events	1,108	14	SHR=2.93 (1.02–8.45)	0.046
30-day landmark analysis	Composite endpoint	1,108	128	2.54 (1.78–3.63)	<0.001
	Thrombotic events	1,108	108	2.51 (1.70–3.71)	<0.001
	Bleeding events	1,108	14	2.99 (1.04–8.61)	0.043
	Death during readmission	1,108	15	3.57 (1.29–9.86)	0.014

Note: HR, hazard ratio; SHR, subdistribution hazard ratio; CI, confidence interval. The event counts in the competing-risk analysis (113 thrombotic events, 14 bleeding events) are lower than in Table 2 (118 and 16) because 5 thrombotic events and 2 bleeding events occurred in patients who died during follow-up and are not counted as first events when death is treated as a competing event.

Supplementary Table S2. Full multivariable Cox models for all endpoints (n=899)

Variable	Composite endpoint HR (95%	P	Thrombotic events HR	P	Major bleeding HR (95%	P	Death during readmission	P

	CI)		(95% CI)		CI)		HR (95% CI)	
Abnormal D-dimer (vs. normal)	**1.64 (1.09–2.47)**	**0.017**	**2.02 (1.30–3.15)**	**0.002**	**1.46 (0.44–4.90)**	**0.538**	**1.73 (0.54–5.52)**	**0.352**
Age (per 1-year increase)	0.99 (0.97–1.02)	0.668	1.00 (0.97–1.02)	0.730	1.00 (0.93–1.07)	0.928	1.03 (0.96–1.11)	0.436
Female (vs. male)	0.78 (0.50–1.22)	0.275	0.84 (0.52–1.37)	0.486	0.53 (0.11–2.60)	0.433	0.68 (0.16–2.86)	0.595
CHA_2DS_2-VASc (per 1-point increase)	1.18 (0.98–1.40)	0.072	1.12 (0.92–1.36)	0.252	0.97 (0.55–1.73)	0.918	1.24 (0.75–2.06)	0.395
HAS-BLED (per 1-point increase)	1.14 (0.92–1.41)	0.243	1.07 (0.85–1.35)	0.572	1.74 (0.86–3.53)	0.124	1.40 (0.72–2.72)	0.326
Hypertension	0.54 (0.34–0.87)	0.011	0.75 (0.45–1.25)	0.269	0.17 (0.04–0.71)	0.016	0.45 (0.09–2.21)	0.322
Chronic heart failure	0.63 (0.36–1.11)	0.111	0.33 (0.15–0.72)	0.006	1.05 (0.24–4.60)	0.953	4.79 (1.33–17.22)	0.017
Myocardial infarction history	1.07 (0.59–1.94)	0.816	0.92 (0.46–1.84)	0.817	0.73 (0.13–3.98)	0.713	4.25 (0.97–18.51)	0.054
Stroke history	0.85 (0.55–1.32)	0.467	1.07 (0.68–1.69)	0.762	0.40 (0.08–2.04)	0.271	0.47 (0.10–2.24)	0.346
Coronary artery disease	1.21 (0.71–2.06)	0.492	1.35 (0.74–2.46)	0.332	4.64 (0.50–43.12)	0.177	0.43 (0.09–2.13)	0.304
Hepatic dysfunction	2.04 (0.71–5.85)	0.184	2.29 (0.69–7.59)	0.176	—		3.08 (0.25–38.33)	0.382

Renal dysfunction	2.85 (1.82–4.46)	<0.001	2.24 (1.34–3.76)	0.002	8.98 (2.52–31.96)	<0.001	3.58 (0.98–13.16)	0.054

Note: HR, hazard ratio; CI, confidence interval. —, not estimable (no events or too few events).