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The impacts of prophylactic anticoagulation therapy during hospitalization on long-term cardiovascular outcomes in high-risk COVID-19 patients amid the omicron wave of the pandemic

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ABSTRACT

Background: Although prophylactic anticoagulation therapy is suggested to be adopted in severe COVID-19 patients, its effects on the long-term cardiovascular (CV) outcomes, namely the risk of major adverse CV events (MACEs) in high-risk CV patients amid the omicron wave of the pandemic, remain unknown.

Methods: We conducted this prospective cohort study of consecutive adults hospitalized COVID-19 between 19 April and 12 June 2022, COVID-19 patients with at least two CV risk factors or pre-existing CV diseases were enrolled. A propensity score matching(PSM) method was used to evaluated the effects of prophylactic anticoagulation therapy in hospital on long-term MACEs, including CV death, non-fatal myocardial infarction, non-fatal stroke, hospitalization due to unstable angina pectoris, coronary revascularization and arterial or venous thrombosis.

Results: Two cohorts (with or without anticoagulants during hospitalization) of each 230 patients with balanced baseline characteristics were formed using PSM. During the 15-month follow-up period, 13 patients with anticoagulants and 29 patients without anticoagulants developed MACEs. Overall, the anticoagulation group had a significantly lower risk of MACEs than the control group (hazard ratio [HR] 0.431; 95 % confidence interval [CI]: 0.224–0.830, P = 0.010). Regarding specific constituents of MACEs, the differences were mainly reflected in arterial or venous thrombosis. The significantly lower HRs of overall MACEs were significantly observed in subgroup of age > 75 years, women, higher D dimer level, unvaccinated and non-nirmatrelvir–ritonavir prescribed patients.

Conclusions: Prophylactic anticoagulation therapy during hospitalization was effective in reducing long-term MACEs among COVID-19 patients with CV risk factors or pre-existing CV diseases amid the omicron wave of the pandemic.

1. Introductions

Corona virus disease 2019 (COVID-19) may be involved in the initiation and activation of the endothelial cell and coagulation cascade, particularly in the presence of predisposing factors, which mostly manifests as thromboembolic events damaging multiple organs [1,2], resulting in an elevated risk of arterial or venous thrombosis of up to 30 % in patients with concomitant cardiovascular (CV) disease [3–6]. Thus, according to some scientific data, healthcare clinicians have taken the responsibility to use therapeutic antithrombotic agents, such as low-molecular-weight heparin (LMWH) or new oral anticoagulants (NOAC), to reduce the severity of COVID-19 by minimizing thrombotic formation [6,7]. Prior studies of anticoagulation treatment in patients with COVID-19 have reported conflicting results [8–14]. COVID-19 patients with CV disease tend to evolve into critical condition or have a poor prognosis. And information on the prognosis of patients with concomitant CV disease regularly using anticoagulants before being presented to the clinics complaining of COVID-19 symptoms is also debatable [15], and more evidence are required to investigate the valuable outcomes of the use of anticoagulants in this population, especially amid the omicron wave of the pandemic.

We conducted this cohort study to evaluate the effects of anticoagulants in hospitalized adult COVID-19 patients with CV risk factors or pre-existing CV diseases. A propensity score matching method was used

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to form two matched cohorts with and without receiving anticoagulants during hospitalization.

2. Materials and methods

2.1. Data source and study population

We conducted this prospective cohort study of consecutive adult patients (age > 18 years) admitted with COVID-19 to Shanghai ninth people's hospital between April 19, 2022 and June 12, 2022. The diagnosis of SARS-CoV-2 infection was considered positive when the reverse transcription polymerase chain reaction (PCR) of the SARS-CoV-2 assay was detected from a nasopharyngeal swab during the Omicron wave of the pandemic. The study was carried out considering the ethical guidelines of the Declaration of Helsinki and received the corresponding vote through the local ethic committee (SH9H-2022-T146-2). All patients provided written informed consent.

CV risk factors were defined as a recorded clinical diagnosis of hypertension, diabetes mellitus, hyperlipidemia, or self-reported smoking status, in the absence of documented CV diseases. Pre-existing CV diseases included coronary artery disease (CAD), heart failure, stroke or peripheral arterial disease (PAD). COVID-19 patients with ≥ 2 CV risk factors in the absence of documented CV disease or ≥ 1 pre-established CV disease were enrolled in the study. We excluded patients who had a prior diagnosis of any major adverse CV events (MACEs) 6 months before the index date and those who died within 30 days after the index date. Patients with therapeutic anticoagulation indication, such as atrial fibrillation, venous thromboembolism (VTE), etc, were also excluded.

Data were also collected for age, sex, body mass index (BMI), non-CV comorbidities, and clinical examination and routinely collected blood results on admission. Myocardial injury was defined as the elevation of high sensitivity cardiac troponin I (hs-cTnI) levels > 99th percentile of the upper reference limit (>0.03 ng/mL for a normal population). If TNI increased, we continuously monitored and obtained its maximum value during hospitalization. Propensity score matching was used in this study to ensure that the anticoagulation and non-anticoagulation cohorts were comparable in terms of demographic characteristics, comorbidities, physical examination and laboratory data results as previous study described [16]. A standard difference of less than 0.1 indicates good matching.

2.2. Follow-up and study outcomes

All patients received a clinical follow-up by telephonic interview and/or clinical visit every 3 months from hospital discharge. The primary efficacy outcome was time to first occurrence of a composite of CV death, non-fatal myocardial infarction, non-fatal stroke, hospitalization due to unstable angina pectoris, coronary revascularization and arterial or venous thrombosis through 15 months. Hospital admission date was used as the start of follow-up.

2.3. Statistical analysis

Statistical analysis was performed using SPSS Statistical Software, version 22.0 (SPSS Inc., Chicago, IL, USA) and R Statistical Software, Version 3.0.1 (the R Foundation for Statistical Computing). Arithmetic means ± standard deviations were calculated for quantitative variables while qualitative variables were given as frequency and percentage (%). For quantitative variable analysis, *t* test and one way ANOVA test, if appropriate, were used. A two-sided Chi square test was used to compare qualitative variables. Univariate and multivariate Cox regression analyses of relevant variables were performed to identify predictors for the occurrence of MACEs. All predictors with a significance of P < 0.10 in the univariate analysis and mandatory inclusion variables considered to be important predictors of clinical endpoints were entered into the multivariate model. Relative risks are expressed as hazard ratios (HR) with 95 % confidence intervals (CIs). Freedom from MACEs at 15 months was analyzed with Kaplan–Meier statistics, with difference between the groups assessed using the log-rank test. All values were two-tailed, and a P value < 0.05 was considered statistically significant.

3. Results

A flowchart of patient enrollment from the COVID-19 cohort was shown in Fig. S1. The cohort included 1142 participants, of which 274 were administered anticoagulants during hospitalization. The remaining 868 formed the control group, they received no anticoagulation therapy. The patient demographic and health characteristics before and after propensity score matching are shown in Tables1 and 2. Before matching, the study group was predominantly older than the control group (76.1

Table 1
Baseline characteristic before propensity score matching.

	non-anticoagulation	anticoagulation	*P* value
	(n = 868)	(n = 274)	
age, years	73.7 ± 12.5	76.1 ± 13.9	0.014
male sex	437(50.3)	145(52.9)	0.457
smoking	257 (29.6)	67 (24.5)	0.131
body mass index, kg/m^2	23.5 ± 4.2	23.7 ± 4.1	0.429
systolic pressure, mm Hg	129.7 ± 11.4	129.3 ± 13.0	0.664
diastolic pressure, mm Hg	78.0 ± 8.5	78.6 ± 8.6	0.278
comorbidity			
hyperlipidemia	323(37.2)	98(35.8)	0.665
hypertension	648 (74.7)	200 (73.0)	0.583
diabetes	311 (35.8)	209(76.3)	0.237
coronary heart disease	323 (37.2)	101(36.7)	0.917
heart failure	42(4.8)	19(6.9)	0.179
cerebrovashcular disease	217 (25.0)	86(31.4)	0.037
peripheral arterial disease	17(2.0)	11 (4.0)	0.055
COPD	21(2.4)	6(2.2)	0.827
malignancy	79 (9.1)	21 (7.7)	0.463
COVID-19 clinical classification			
mild	740 (85.3)	239 (87.2)	0.662
moderate	102 (11.8)	29 (10.6)	
severe or critical	26 (3.0)	6(2.2)	
laboratory results			
white blood cell count, × 10^9/L	5.6 ± 1.8	6.2 ± 2.6	<0.001
neutrophil count, × 10^9/L	3.4 ± 1.5	4.2 ± 2.7	<0.001
lymphocyte count, × 10^9/L	1.5 ± 0.6	1.3 ± 0.6	<0.001
hemoglobin, g/L	126.7 ± 19.6	121.1 ± 22.7	<0.001
platelet count, × 10^9/L	197.0 ± 66.9	200.8 ± 80.3	0.482
C-reactive protein, mg/L	13.3 ± 17.4	21.7 ± 22.5	<0.001
ALT, μ/L	24.4 ± 14.9	27.2 ± 28.7	0.120
total bilirubin, mmol/L	12.2 ± 7.5	12.5 ± 6.7	0.551
albumin, g/L	38.5 ± 4.7	36.7 ± 5.4	<0.001
potassium, mmol/L	3.9 ± 0.5	3.9 ± 0.6	0.329
eGFR, mL/min/1.73 m2	74.6 ± 22.3	69.5 ± 25.7	0.004
troponin I peak, ng/mL	0.030 ± 0.128	0.041 ± 0.170	0.239
troponin I (>0.03 ng/mL)	69 (7.9)	45(16.4)	<0.001
procalcitonin, ng/mL	0.51 ± 1.33	1.06 ± 3.25	0.007
D-dimer, mg/L	0.69 ± 0.94	2.10 ± 5.16	<0.001
BNP, pg/mL	112.3 ± 237.9	166.1 ± 295.4	0.006
ESR, mm/h	26.5 ± 15.1	27.6 ± 16.3	0.304
treatment			
nirmatrelvir/ritonavir	346(39.9)	158(57.7)	<0.001
intravenous antibiotics	161 (18.5)	43(15.7)	0.282
use of corticosteroid	59(6.8)	23 (8.4)	0.372
use of intravenous immune globulin	25(2.9)	9(3.3)	0.731
vaccination			
unvaccinated	571 (65.8)	176 (64.2)	0.315
partial vaccinated	152 (17.5)	42 (15.3)	
full vaccinated	145 (16.7)	56 (20.4)	
admission to intensive care unit	39(4.5)	8 (2.9)	0.253

COPD: chronic obstructive pulmonary disease; COVID: corona virus disease; ALT: alanine transaminase; eGFR: estimated glomerular filtration rate; BNP: brain natriuretic peptide; ESR: erythrocyte sedimentation rate.

Table 2
Baseline characteristic after propensity score matching.

	non-anticoagulation	anticoagulation	*P* value
	(n = 230)	(n = 230)	
age, years	76.4 ± 11.1	75.7 ± 13.5	0.535
male sex	121(52.6)	122(53.0)	0.926
smoking	57 (24.8)	55 (23.9)	0.828
body mass index, kg/m^2	23.8 ± 4.5	23.6 ± 4.2	0.634
systolic pressure, mm Hg	129.0 ± 12.4	129.0 ± 12.3	0.994
diastolic pressure, mm Hg	77.3 ± 8.6	77.6 ± 8.6	0.752
comorbidity			
hyperlipidemia	78(33.9)	81(35.2)	0.769
hypertension	163 (70.7)	166 (72.2)	0.757
diabetes	82 (35.7)	92(40.0)	0.336
coronary heart disease	86 (37.4)	87(37.8)	0.923
heart failure	16(7.0)	16(7.0)	1.000
cerebrovashcular disease	77(33.5)	70(30.4)	0.484
peripheral arterial disease	6(2.6)	9(3.9)	0.431
COPD	5(2.2)	5(2.2)	1.000
Malignancy	18 (7.8)	19 (8.3)	0.864
COVID-19 classification			
mild	202(87.8)	199 (86.5)	0.603
moderate	23 (10.0)	28 (12.2)	
severe or critical	5 (2.2)	3(1.3)	
laboratory results			
white blood cell count, × 10^9/L	5.8 ± 2.0	6.0 ± 2.4	0.256
neutrophil count, × 10^9/L	3.7 ± 1.7	4.0 ± 2.2	0.143
lymphocyte count, × 10^9/L	1.4 ± 0.6	1.3 ± 0.6	0.104
hemoglobin, g/L	124.7 ± 20.7	122.2 ± 21.9	0.209
platelet count, × 10^9/L	193.7 ± 64.2	195.8 ± 75.5	0.745
C-reactive protein, mg/L	18.8 ± 22.1	19.8 ± 18.7	0.587
ALT, μ/L	23.5 ± 13.6	25.8 ± 27.5	0.272
total bilirubin, mmol/L	12.0 ± 5.2	12.3 ± 6.6	0.573
albumin, g/L	38.0 ± 5.0	37.3 ± 5.1	0.154
potassium, mmol/L	3.9 ± 0.5	3.9 ± 0.6	0.971
eGFR, mL/min/1.73 m2	73.4 ± 21.1	70.8 ± 25.4	0.240
troponin I peak, ng/mL	0.037 ± 0.132	0.029 ± 0.085	0.437
troponin I (>0.03 ng/mL)	19 (8.3)	30(13.0)	0.096
procalcitonin, ng/mL	0.56 ± 1.66	0.77 ± 1.43	0.152
D-dimer, mg/L	1.04 ± 1.46	1.36 ± 4.96	0.344
BNP, pg/mL	113.0 ± 180.0	143.5 ± 257.0	0.141
ESR, mm/h	25.1 ± 13.1	27.5 ± 15.8	0.069
treatment			
nirmatrelvir/ritonavir	107(46.5)	125(54.3)	0.093
intravenous antibiotics	36 (15.7)	31(13.5)	0.509
use of corticosteroid	16(7.0)	15 (6.5)	0.852
use of intravenous immune globulin	5(2.2)	5(2.2)	1.000
vaccination			
unvaccinated	147(63.9)	145(63.0)	0.461
partial vaccinated	44(19.1)	47(20.4)	
full vaccinated	39(17.0)	48(20.9)	
admission to intensive care unit	14 (6.1)	6 (2.6)	0.067

COPD: chronic obstructive pulmonary disease; COVID: corona virus disease; ALT: alanine transaminase; eGFR: estimated glomerular filtration rate; BNP: brain natriuretic peptide; ESR: erythrocyte sedimentation rate.

± 13.9 vs. 73.7 ± 12.5 years). Concerning comorbidities, the anticoagulation group had more patients with cerebrovascular disease than the control cohort. Additionally, the anticoagulation group had higher levels of neutrophil count, C-reactive protein (CRP), D dimer, procalcitonin and brain natriuretic peptide (BNP), and lower levels of lymphocyte count, hemoglobin, albumin and estimated glomerular filtration rate (eGFR). After propensity score matching, two matched cohorts, each of 230 patients, were identified. The absolute standardized differences between the anticoagulation and the control group were less than 0.1, indicating a high level of balance between the two groups. Among the 460 patients who underwent propensity score matching, the median age was 76 years old, 47 % were female (Table 2). In the anticoagulation group, 209 patients received LMWH and 21 received NOAC, and the anticoagulation time was 5.2 ± 1.7 days.

The primary efficacy outcome, evaluated at month 15, occurred in 13 of 230 patients (5.7 %) in the anticoagulation group and 29 of 230 patients (12.6 %) in the control group. The anticoagulation group had a significantly lower risk of MACEs than the control group (hazard ratio [HR], 0.431; 95 % confidence interval [CI]: 0.224–0.830, P = 0.010). Regarding specific constituents of MACEs, the differences were mainly reflected in arterial or venous thrombosis (6 [2.6 %] vs. 16 [7.0 %], P = 0.029) but without differences in the incidences of CV death (2 [0.9 %] vs. 3 [1.3 %], P = 1.000), non-fatal myocardial infarction (3 [1.3 %] vs. 5[2.2 %], P = 0.724), non-fatal stroke (3 [1.3 %] vs. 9 [3.9 %], P = 0.079), hospitalization due to unstable angina pectoris (4 [1.7 %] vs. 7 [3.0 %], P = 0.360), and coronary revascularization (5 [2.2 %] vs. 11 [4.8 %], P = 0.127).

At multivariate Cox regression analysis, myocardial injury (troponin I peak, HR 3.563, 95 %CI [1.510–8.518]: P = 0.012), COVID-19 clinical severity (HR 2.137, 95 %CI: 1.252–3.467, P = 0.005) were the independent risk factors, and anticoagulation therapy (HR 0.479, 95 % CI: 0.246–0.933, P = 0.030) was the independent protective factor for the occurrence of MACEs in this population (Fig. 1). Comparisons of the Kaplan–Meier curves by log-rank test showed that patients with anticoagulants had a higher freedom-from MACEs survival rate (P = 0.001, Fig. 2) compared to those without anticoagulants.

Subgroup analyses were conducted according to age stratification, gender difference, D dimer level, vaccination status and the prescription of nirmatrelvir-ritonavir. The significantly lower risks of overall MACEs benefited from anticoagulation therapy were observed in subgroup of age > 75 years, women, higher D dimer level (>1 mg/L), unvaccinated and non– nirmatrelvir–ritonavir prescribed patients (Figs. S2–S6).

Of high-risk patients enrolled in the present study, anticoagulation therapy exerted more benefits in patients with pre-existing CV disease (22/149 vs 10/147, P = 0.027) instead of with ≥ 2 CV risk factors (7/81 vs 3/83, P = 0.179). In patients prescribed with anticoagulants, there was no markedly difference with regard

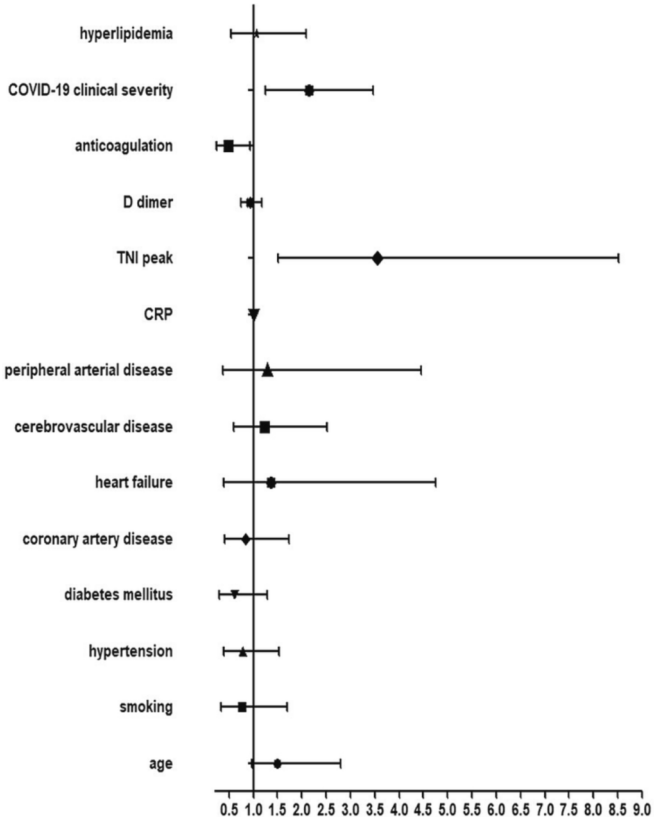

Fig. 1. Forest plot of multivariate Cox regression analysis. CRP: C-reactive protein; TNI: troponin I.

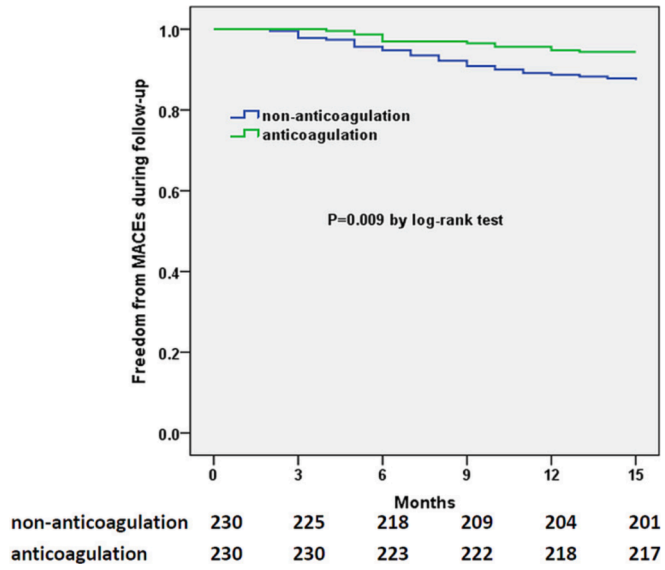

Fig. 2. Survival Kaplan–Meier curve for MACEs, according to the presence or absence of anticoagulation therapy during the index hospitalization for COVID-19.

to the anticoagulation benefit among different types of pre-existing CV diseases (P = 0.737). Besides, there was no significant difference in clinical benefit of anticoagulation therapy in patients with mild (eGFR ≥ 30 mL/min/1.73 m^2 and < 60 mL/min/1.73 m2) or severe (eGFR < 30 mL/min/1.73 m^2) renal dysfunction (P = 0.584).

No critical-site or fatal bleeding events were observed in either study group. No major bleeds were observed in both anticoagulation and control group. Clinically relevant nonmajor bleeding was also not frequent in anticoagulation group than control group (1.7 % versus 0.87 %, P = 0.685).

4. Discussion

In this propensity scoring match cohort study, our result indicated that prophylactic anticoagulation therapy during hospitalization was effective in reducing long-term MACEs among COVID-19 patients with pre-established CV disease or CV risk factors, particularly when treated in patients aged > 75 years, female, high D dimer, unvaccinated or non-nirmatrelvir–ritonavir prescribed patients amid the omicron wave of the pandemic.

Although the pathogenicity and clinical severity of Omicron appear to be weakened compared with previous variants, the number of hospital admissions and CV complications due to Omicron might still be substantial, depending on the extent to which age, vaccination status, and comorbidities. Growing clinical evidences have reported that arterial or venous thrombosis were frequently concurrent with COVID-19 due to the hypercoagulable condition [3–6]. Patients with COVID-19 frequently experience higher D-dimer plasma levels, mildly reduced platelet production, and slightly extended prothrombin times. In 2020, published data indicated that 46 % of all patients with COVID-19 from China had D-dimer levels > 0.5 mg/L. Similarly, a research in patients with COVID-19 in Wuhan showed that 42 % of all patients who died had D-dimer levels > 1 mg/L, which was linked to an 18-fold higher probability of death [17–19].

SARS-CoV-2 infection directly alters the endothelium and coagulation function, both of which have been linked to CV diseases. While the mechanisms are unclear, a few isolated case reports have linked COVID-19 to exposure of thrombogenic molecules or proinflammatory cytokines, and individual with a history of CV diseases may be at a meaningfully increased risk of thrombo-vascular complications after COVID-19 infection [20,21]. Furthermore, untreated patients with COVID-19 may cause a cytokine storm in which the immune system overproduces pro-inflammatory substances such as tumor necrosis factor-α and interleukins, and resulting in an activation of coagulation patterns [3,4].

Thus, anticoagulants have been primarily ordered for severe COVID-19 patient treatment. However, information on the prognosis of COVID-19 patients with concomitant CV disease regularly using anticoagulants is still debatable, and more evidence are needed to investigate the valuable outcomes of the use of anticoagulants in these patients [8–15]. The association of systemic anticoagulation with extended survival of hospitalized patients with COVID-19 demonstrated no statistical significance according to a previous cohort study. While the overall proportion of mortality between the two cohorts was comparable, the median duration of survival of patients who received anticoagulation was better than those of individuals with concomitant CV disease who did not receive prior anticoagulant therapy [22]. Another study conducted in China found that LMWH treatment decreased the death rate in individuals with COVID-19-associated coagulopathy. However, the direct-acting anticoagulation agents such as vitamin K antagonist (VKA) and unfractionated heparin had not been to clearly shown to protect against thrombotic events or reducing severity of COVID-19 [23]. Thromboprophylaxis with enoxaparin did not reduce early hospitalizations and deaths among outpatients with symptomatic COVID-19 [24]. In adult community patients with COVID-19, early thromboprophylaxis with enoxaparin did not improve the course of COVID-19 neither in terms of hospitalization and death nor considering COVID-19-related symptoms [25]. The ETHIC trial also suggested that prophylaxis with LMWH had no benefit for at-risk outpatients with COVID-19 [26]. However, in patients at high risk discharged after hospitalization due to COVID-19, thromboprophylaxis with rivaroxaban 10 mg/day for 35 days improved clinical outcomes compared with no extended thromboprophylaxis [27].

As COVID-19 is a current worldwide concern with greater mortality particularly in those with CV diseases, and our study addressed the outcomes of anticoagulant therapy during hospitalization in patients with COVID-19 with CV risk factors or pre-existing CV diseases. We believe that patients with COVID-19 are susceptible to CV comorbidities, mainly hypercoagulability, and a pro-inflammatory state. Management of these patients requires a complete understanding of the pathogenesis of these comorbidities. CV risk factors such as hypertension and diabetes, and chronic CV diseases (CVD), including ischaemic heart disease and heart failure, are highly prevalent among patients admitted to hospital with COVID-19 [28,29]. In population-based studies, diabetes and chronic CV disease, but not hypertension, have been associated with higher mortality [30,31]. At present, patients with either pre-established CV disease or CV risk factors are considered to be vulnerable individuals. And we found that prophylactic anticoagulation therapy during hospitalization in this population was effective for the prevention from MACEs during the long-term follow-up after discharge. If anticoagulants are to be used, DOACs are favored due to their better action and lesser side effects compared with other anticoagulant agents such as VKAs [15]. Further research is required to describe the best course and optimal dose of anticoagulant use in the treatment of patients with COVID-19 with comorbidities such as CV disease.

In the present study, the main benefits of anticoagulants were older than 75 years of age. For patients > 75 years of age, there were more comorbidities or risk factors, to be more likely to develop thromboembolism. The benefit for MACEs reduction was mainly in female patients, another study also indicated that elderly women with atrial fibrillation benefited more than men from anticoagulation therapy [32]. D dimer elevation reflects a hypercoagulable condition, and the benefit of anticoagulant in this study was mainly reflected in patients with high-level D dimer. Previous study showed that nirmatrelvir-ritonavir was effective in reducing long-term MACEs among non-hospitalized patients with COVID-19 [33], and COVID-19 patients who are not prescribed for nirmatrelvir–ritonavir might have a higher relative risk of adverse CV

events and are therefore more likely to benefit from anticoagulation therapy. Our study also suggested that the anticoagulation benefit is mainly reflected in unvaccinated patients compared with partially or completely immunized patients. Either partial or complete vaccination was showed to be associated with a lower risk of MACEs after SARS-CoV-2 infection [34]. Unvaccinated COVID-19 patients have a higher relative risk of adverse CV events and are more likely to benefit from anticoagulant therapy.

Some limitations of our study should be acknowledged. First, this was a single center study, potentially limiting external validity, so an adequately powered, randomized clinical trial is needed. Second, we cannot exclude all sources of confounding or selection biases in spite of propensity score matching used. Third, we could not verify whether the improvement in the incidence of MACEs was solely attributable to anticoagulation therapy. At last, we did not perform a sequencing procedure for SARS-Cov2 testing for each patient, and we assumed the Omicron variant infection on an epidemiological basis.

5. Conclusions

In conclusion, prophylactic anticoagulation therapy during hospitalization was effective in reducing long-term MACEs among COVID-19 patient with CV risk factors or pre-existing CV disease amid the Omicron wave of the pandemic. These findings suggest the potential role of anticoagulation therapy as a preventive measure to reduce further adverse CV outcomes in this high-risk population.

Author contributions

JG: concept of the study, design, data analysis, interpretation of the results, and drafting of the manuscript. YW: data analysis, interpretation of the results. JFZ: data extraction and interpretation. CQW: infrastructure support, data interpretation. All authors agreed with the final version of the manuscript.

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CRediT authorship contribution statement

Jun Gu: Conceptualization, Funding acquisition, Methodology, Project administration, Writing – original draft. **Yue Wang:** Data curation, Formal analysis. **Jun-feng Zhang:** Data curation, Formal analysis, Investigation. **Chang-qian Wang:** Conceptualization, Methodology, Resources, Supervision, Validation, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2024.101353.

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