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Association of chronic anticoagulant and antiplatelet use on disease severity in SARS-COV-2 infected patients

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Highlights

- We evaluated clinical outcomes in over 28,000 SARS-CoV-2 infected patients.
- We did not find an association between chronic antiplatelet and anticoagulant use with reduced risk of hospitalization, mechanical ventilation, thrombosis or mortality.

Introduction

Emerging evidence suggests that SARS-CoV-2 coronavirus associated coagulopathy is associated with higher morbidity and mortality [1–3]. To mitigate this, there has been increased interest and clinical use of empiric anticoagulation and antiplatelet therapy. However, it is unclear if anticoagulants or antiplatelets given in patients prior to their SARS-CoV-2 infection influences disease severity. We report outcomes of SARS-CoV-2 infected patients prescribed anticoagulants or antiplatelets for preexisting conditions within Kaiser Permanente Northern California (KPNC), a large integrated health system serving 4.4 million members.

Methods

This retrospective cohort study included KPNC adult members (≥ 18 years) with positive SARS-CoV-2 testing between February 25, 2020, and July 31, 2020. Patients were stratified based on electronic medical records indicating a filled prescription or actively taking antiplatelets or anticoagulants within 90 days prior to SARS-CoV-2 diagnosis.

Primary outcomes included emergency department (ED) visit, inpatient hospitalization, intensive care unit (ICU) stay, venous thromboembolism (VTE), mechanical ventilation, and mortality between date of SARS-CoV-2 diagnosis and the first of either 45 days after diagnosis or 8/17/2020. Any severe outcome was defined as any of inpatient hospitalization, mechanical ventilation, or mortality. Logistic regression was used to calculate odds ratios and 95% confidence intervals (CI) for the association of anticoagulants or antiplatelets with primary outcomes, adjusting for sociodemographic and clinical characteristics. Models were adjusted for week of diagnosis given changing testing and treatment guidelines over time.

The Research Determination Committee for KPNC has determined the project does not meet the regulatory definition of research involving human subjects per 45 CFR 46.102(d).

Results/discussion

Of 28,076 patients with confirmed positive SARS-CoV-2 infection, 720(3%) were on antiplatelets, 255(1%) were on anticoagulants, and 49(< 1%) were on both. The most common antiplatelet medications were aspirin (N = 679) and clopidogrel (N = 147). The most common anticoagulants were coumadin (N = 130) and dabigatran (N = 119). Most patients on anticoagulants or antiplatelets were older (71% for anticoagulant; 66% for antiplatelet aged ≥ 60 years), non-white (55%; 68%), overweight or obese (80%; 76%), and

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Table 1 Sociodemographic and clinical characteristics of 28,076 adult SARS-COV-2 positive patients diagnosed between 2/25/2020 and 7/31/2020

	Patients with anticoagulant use with or without antiplatelet use N = 304 N (%)	Patients with antiplatelet use N = 720 N (%)	Patients without anticoagulant or antiplatelet use N = 27,052 N (%)
Age (years)			
18–39	19 (6)	50 (7)	13,118 (48)
40–49	15 (5)	47 (7)	5596 (21)
50–59	55 (18)	147 (20)	4484 (17)
60–69	59 (19)	202 (28)	2505 (9)
70–79	79 (26)	139 (19)	846 (3)
80+	77 (25)	135 (19)	503 (2)
Median (IQR)	70 (58–80)	66 (55–77)	41 (30–53)
Sex			
Male	166 (55)	385 (53)	13,030 (48)
Female	138 (45)	335 (47)	14,022 (52)
Race/ethnicity			
African American	28 (9)	93 (13)	1895 (7)
Asian	24 (8)	105 (15)	2947 (11)
Hispanic	89 (29)	232 (32)	13,769 (51)
White	138 (45)	232 (32)	5374 (20)
Missing/other	25 (8)	58 (8)	3067 (11)
Body mass index[a]			
Underweight	9 (3)	12 (2)	184 (1)
Healthy weight	51 (17)	153 (21)	4583 (17)
Overweight	89 (29)	215 (30)	7770 (29)
Obese	153 (50)	331 (46)	11,523 (43)
Median (IQR)	30 (26–36)	29 (25–35)	30 (26–34)
Charlson comorbidity index			
0	37 (12)	111 (15)	20,434 (76)
1–2	86 (28)	224 (31)	5199 (19)
≥ 3	181 (60)	385 (53)	1419 (5)
Median (IQR)	3 (1–6)	3 (1–5)	0 (0–0)
Hypertension	154 (51)	342 (48)	1538 (6)
Diabetes	114 (38)	325 (45)	1880 (7)
Ever smoker[a]	148 (49)	333 (46)	6170 (23)
Any outcome[b]	174 (57)	366 (51)	7373 (27)
Any severe outcome[c]	118 (39)	253 (35)	2582 (10)
Venous thromboembolism outcome	22 (7)	16 (2)	196 (1)

IQR Interquartile range

[a]Includes information for up to 10 years prior to diagnosis and patients with missing information

[b]Any outcome includes any of inpatient, invasive ventilator, death, thrombotic event, emergency department, and intensive care unit

[c]Any severe outcome includes any of inpatient, invasive ventilator, and death

had ≥ 3 comorbidities (60%; 53%) (Table 1). Of the patients on chronic anticoagulation, 15% had a prior venous thrombotic event, 65% had atrial fibrillation and 40% had coronary artery disease. Of the patients on chronic antiplatelet therapy, 3% had a prior venous thrombotic event, 10% had atrial fibrillation and 40% had coronary artery disease and 20% had congestive heart failure. The median time from SARS-CoV-2 positivity to each primary outcome was as follows: inpatient admission 2 days, invasive ventilation 5.5 days, death 12 days, VTE 3 days, emergency department 0 days (the site of testing for many patients), ICU admission 3 days, any outcome 0 days, and any severe outcome 2 days.

After adjusting for sociodemographic and clinical characteristics, chronic anticoagulants or antiplatelets use—was not associated with a lower risk of any primary outcome, including VTE, ED visit, ICU stay invasive ventilator use or any outcome (OR anticoagulants vs none 1.21, CI 0.93–1.56; OR antiplatelets vs none 0.96, CI 0.81–1.14). Older patients had an increased risk of all outcomes, with the highest risk of severe outcomes in those ≥ 80 years compared to 18–29 years (OR 21.07, CI 16.40–27.07). Male patients and African American, Asian, and Hispanic patients (compared to white patients) also had increased risk of severe outcomes. Increased mortality risk was noted in patients with hypertension (OR 1.98, CI 1.54–2.56), but not with diabetes (OR 1.19, CI 0.91–1.57) or obesity (OR 1.24, CI 0.92–1.67). (Table 2).

This analysis using a socio-demographically diverse cohort of patients demonstrated no association with improved outcomes of hospitalization, mortality or mechanical ventilation patients on chronic anticoagulants or antiplatelets prior to SARS-CoV-2 diagnosis. There was a significantly higher risk of severe outcomes in those with older age, African, Asian or Hispanic ethnicity, male gender, obesity, diabetes and hypertension.

Infection with SARS-CoV-2 can lead to a severe systemic inflammatory response, vascular endothelial dysfunction and hemostatic derangements, predisposing to microvascular and macrovascular thrombi and significant morbidity [1, 4]. Efforts to mitigate the disease severity have generated discussions regarding empiric use of anticoagulants and antiplatelets in SARS-CoV-2 infected patients, though with little substantive data on benefit [1, 5, 6]. A recent study in SARS-CoV-2 infected patients in a New York City health system showed no difference in survival, time to mechanical ventilation or hospital admission in those patients who were on anticoagulant or antiplatelet therapy at the time of SARS-CoV-2 diagnosis [7]. Our study in a diverse group of SARS-CoV-2 infected patients in Northern California also did not show an association between chronic anticoagulant and antiplatelet use with mortality, invasive ventilator use or inpatient hospitalizations. A recent study of European patients found lower survival and increased mortality risk in patients on chronic anticoagulation at the time of hospital admission for SARS-CoV-2 infection, though the prevalence of several comorbidities was high in that cohort [8]. The conflicting results likely arise from differences in patient population with the New York and European patients being more severely ill with overall higher risk of hospitalization during the peak of illness in the spring of 2020. Our population included a larger cohort of SARS-CoV-2 patients, the majority with mild disease and may be more representative of actual SARS-CoV-2 infection given expansion of testing over time. While our study did not show a protective effect of the chronic use of these agents in mitigating disease severity, there may still be certain subgroups of patients that may benefit from the use of anticoagulation or antiplatelet therapy. Given these inconsistent findings however, we suggest reticence in broad empiric use of these agents at SARS-CoV-2 diagnosis until prospective studies powered to evaluate thrombosis risk and clinical outcomes with value to patients and health care systems are completed.

Similar to prior studies, we also saw significant associations between sociodemographic factors and increased severity of disease in SARS-CoV-2 infected patients. Specifically, patients of older age and male gender had increased risk of any severe outcome [9]. Our findings also showed significant disparities in risk of hospitalizations and invasive ventilator use in patients of ethnic/racial minorities compared to their white counterpart, but did not see racial/ethnic differences in mortality [10, 11]. Our study also confirmed increased disease severity in patients with diabetes, hypertension and obesity though mortality risk was significantly associated only with hypertension [10–12]. Given increasing evidence of the impact of comorbidities, age and race to disease severity, future studies should evaluate resources and treatment protocols that would impact outcomes in these subgroups of patients.

The major strength of this study included the availability of all outcomes data for over 28,000 inpatients and outpatients with SARS-CoV-2 diagnosis over an extended period of time in Northern California. Limitations include possible missed data from undiagnosed SARS-CoV-2 infected patients due to evolving SARS-CoV-2 testing and variance in inpatient treatments, including potential use of anticoagulation and antiplatelet therapy in critically ill patients, which may have influenced outcomes. We also did not have data on laboratory measurements which may have been used to risk stratify patients and guide inpatient treatment. Despite this, we found no association with decreased mortality, hospitalization or mechanical ventilation in patients on anticoagulants and antiplatelets preceding SARS-CoV-2 diagnosis.

Table 2 Logistic regression models for clinical outcomes among 28,076 adult SARS-COV-2 positive patients diagnosed between 2/25/2020 and 7/31/2020*

	IP N = 2,863	Invasive ventilator N = 516	Death N = 396	Venous thromboembolism[a] N = 206	ED N = 7724	ICU N = 797	Any outcome[b] N = 7913	Any severe outcome[c] N = 2953
Medication								
Anticoagulants with or without antiplatelets (N = 304)	1.02 (0.77–1.35)	0.74 (0.44–1.25)	0.95 (0.62–1.46)	1.12 (0.49–2.55)	1.06 (0.82–1.37)	0.98 (0.65–1.47)	1.21 (0.93–1.56)	1.01 (0.76–1.34)
Antiplatelets (N = 720)	0.97 (0.80–1.18)	0.71 (0.50–1.02)	0.89 (0.64–1.24)	0.84 (0.46–1.52)	0.90 (0.76–1.07)	0.83 (0.62–1.12)	0.96 (0.81–1.14)	0.93 (0.76–1.13)
None (N = 27,052)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Age								
18–29	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)[d]	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
30–39	1.72 (1.42–2.08)	1.78 (0.95–3.35)		1.87 (0.83–4.22)	1.20 (1.10–1.32)	1.81 (1.17–2.81)	1.19 (1.09–1.29)	1.68 (1.39–2.03)
40–49	2.67 (2.22–3.20)	3.94 (2.23–6.97)		4.13 (1.98–8.61)	1.65 (1.51–1.80)	3.58 (2.39–5.36)	1.61 (1.47–1.76)	2.62 (2.19–3.13)
50–59	3.80 (3.17–4.55)	8.13 (4.69–14.06)	5.34 (3.23–8.83)	6.16 (2.99–12.71)	1.81 (1.65–1.99)	5.65 (3.81–8.39)	1.74 (1.59–1.91)	3.70 (3.1–4.42)
60–69	5.91 (4.89–7.14)	13.10 (7.52–22.82)	11.15 (6.86–18.12)	7.08 (3.34–15.02)	2.31 (2.07–2.58)	8.36 (5.59–12.52)	2.23 (2.00–2.48)	5.69 (4.72–6.86)
70–79	11.41 (9.14–14.25)	21.22 (11.79–38.17)	26.84 (16.19–44.49)	11.26 (5.01–25.32)	3.46 (2.96–4.05)	14.01 (9.07–21.63)	3.47 (2.97–4.06)	11.41 (9.16–14.20)
80+	16.50 (12.8–21.28)	15.29 (8.02–29.14)	85.96 (51.45–143.62)	8.79 (3.51–21.99)	4.51 (3.71–5.47)	11.41 (7.04–18.49)	5.28 (4.33–6.43)	21.07 (16.40–27.07)
Sex								
Male	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Female	0.64 (0.59–0.7)	0.43 (0.35–0.52)	0.52 (0.41–0.65)	0.44 (0.33–0.60)	0.92 (0.87–0.97)	0.46 (0.39–0.54)	0.94 (0.88–0.99)	0.64 (0.59–0.70)
Race/ethnicity								
African American	1.59 (1.33–1.90)	1.67 (1.17–2.37)	0.97 (0.66–1.43)	1.85 (1.12–3.06)	2.22 (1.97–2.49)	1.65 (1.23–2.23)	2.18 (1.94–2.45)	1.53 (1.28–1.83)
Asian	1.77 (1.51–2.08)	1.78 (1.29–2.46)	0.91 (0.63–1.33)	1.14 (0.68–1.90)	1.31 (1.18–1.47)	1.82 (1.39–2.39)	1.30 (1.17–1.45)	1.68 (1.44–1.96)
Hispanic	1.54 (1.36–1.74)	1.53 (1.18–1.97)	1.02 (0.77–1.34)	1.41 (0.97–2.06)	1.53 (1.42–1.66)	1.73 (1.40–2.14)	1.50 (1.38–1.62)	1.46 (1.29–1.64)
White	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Missing/other	1.13 (0.94–1.36)	1.22 (0.82–1.81)	1.10 (0.73–1.68)	0.62 (0.31–1.28)	0.73 (0.65–0.83)	1.35 (0.97–1.86)	0.72 (0.64–0.81)	1.09 (0.91–1.32)
Body mass index[e]								
Underweight	1.64 (1.06–2.54)	0.54 (0.16–1.82)	1.48 (0.81–2.74)	0.97 (0.22–4.17)	1.66 (1.20–2.31)	1.49 (0.73–3.07)	1.74 (1.25–2.42)	1.83 (1.20–2.80)
Healthy weight	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Overweight	1.15 (0.99–1.33)	1.06 (0.79–1.42)	0.73 (0.54–1.00)	0.74 (0.48–1.14)	1.13 (1.03–1.24)	1.18 (0.92–1.50)	1.15 (1.05–1.26)	1.11 (0.96–1.28)
Obese	1.85 (1.61–2.12)	1.71 (1.29–2.27)	1.24 (0.92–1.67)	1.10 (0.73–1.65)	1.38 (1.26–1.50)	1.70 (1.34–2.15)	1.41 (1.29–1.54)	1.79 (1.56–2.06)

Table 2 (continued)

	IP N = 2,863	Invasive ventilator N = 516	Death N = 396	Venous thromboembolism[a] N = 206	ED N = 7724	ICU N = 797	Any outcome[b] N = 7913	Any severe outcome[c] N = 2953
Charlson comorbidity index								
0	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
1–2	1.12 (1.00–1.26)	1.03 (0.80–1.33)	1.50 (1.06–2.11)	0.91 (0.62–1.33)	1.25 (1.16–1.35)	1.04 (0.84–1.28)	1.25 (1.15–1.35)	1.13 (1.00–1.27)
≥ 3	1.29 (1.09–1.53)	1.12 (0.80–1.56)	2.39 (1.63–3.51)	0.75 (0.44–1.29)	1.43 (1.25–1.64)	1.18 (0.90–1.56)	1.47 (1.28–1.68)	1.38 (1.16–1.63)
Hypertension								
Yes	2.88 (2.53–3.26)	2.53 (2.00–3.20)	1.98 (1.54–2.56)	2.24 (1.53–3.28)	1.99 (1.78–2.23)	2.40 (1.97–2.92)	1.95 (1.74–2.18)	2.72 (2.40–3.09)
No	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Diabetes								
Yes	1.87 (1.63–2.14)	1.72 (1.33–2.22)	1.19 (0.91–1.57)	1.61 (1.07–2.43)	1.41 (1.26–1.58)	2.21 (1.79–2.73)	1.43 (1.28–1.60)	1.86 (1.63–2.13)
No	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Smoking status[e]								
Ever	1.00 (0.91–1.11)	1.07 (0.87–1.32)	1.15 (0.91–1.46)	1.07 (0.78–1.47)	1.08 (1.01–1.16)	1.08 (0.91–1.28)	1.08 (1.01–1.15)	1.01 (0.91–1.11)
Never	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)

[a]Excludes 126 patients with a prior venous thromboembolism (VTE) (N = 27,950) due to difficulty distinguishing prior VTE from new VTE in the electronic medical record

[b]Any outcome includes any of inpatient, invasive ventilator, death, thrombotic event, emergency department, and intensive care unit

[c]Any severe outcome includes any of inpatient, invasive ventilator, and death

[d]Reference group for death outcome is 18–49 years due to lack of outcomes in youngest age groups

[e]Includes information for up to 10 years prior to diagnosis, also adjusts for missing and unknown status

[*]Includes outcomes up to the first of either 45 days after SARS-CoV-2 diagnosis or 8/17/2020

[*]All models are adjusted for age, sex, race/ethnicity, body mass index, Charlson comorbidity index, hypertension, diabetes, and smoking history as well as the week of SARS-COV-2 diagnosis

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Compliance with ethical standard

Conflict of interest The authors have no relevant financial disclosures to disclose.

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