FOLIA MEDICA CRACOVIENSIA
Vol. LXIII, 4, 2023: 99–108
PL ISSN 0015-5616
DOI: 10.24425/fmc.2023.148762

Hypertension and Gastrointestinal Bleed in COVID-19 Patients: Associations with Mortality, Acute Kidney Injury, Vasopressor Use, and Mechanical Ventilation Use

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Abstract: There are mixed findings on the association of hypertension or gastrointestinal bleed (GIB) with mortality in COVID-19 patients but no research on the combination of both hypertension and GIB with mortality in COVID-19 patients. We study in COVID-19 patients the association of hypertension and GIB with mortality, acute kidney injury (AKI), vasopressor use, and/or mechanical ventilation. This is a retrospective study of COVID-19 patients who were categorized into groups of no GIB/no hypertension (n = 653), yes hypertension/no GIB (n = 1,620), yes GIB/no hypertension (n = 104), or yes GIB/yes hypertension (n = 334). Covariates included demographics and medical history variables. In the multivariate logistic regression analysis for the composite outcome of mortality, AKI, vasopressor use, and/or mechanical ventilation use, yes hypertension/no GIB (OR: 1.47, 95% CI: 1.13, 1.89, p <0.001) and yes GIB/no hypertension (OR: 1.68, 95% CI: 1.02, 2.78, p <0.001) were each significantly positively associated with the composite outcome. The yes GIB/yes hypertension group was not significantly associated with the composite outcome. In conclusion, we found that hypertension or GIB alone were each significantly associated with increased odds for the composite outcome while having both hypertension and GIB was protective and not significantly associated with the composite outcome. We recommend that clinicians be aware of such findings when treating patients with COVID-19, as those with both hypertension and GIB may not need as aggressive treatment as compared to those with either hypertension or GIB.

Keywords: Gastrointestinal Hemorrhage, Hypertension, COVID-19.

Submitted: 12-Dec-2023; **Accepted in the final form:** 27-Dec-2023; **Published:** 30-Dec-2023.

Introduction

The prevalence of hypertension (HTN) in the United States ranges from 35–50% [1, 2]. HTN is a common co-morbidity among COVID-19 patients and prevalence ranges from 15.0–36.5% [3, 4]. Also, gastrointestinal bleed (GIB) occurs in 2–13% of patients hospitalized with COVID-19 [5–7]. COVID-19 patients often experience mortality and acute kidney injury (AKI) [8]. COVID-19 patients are often treated with vasopressors and/or mechanical ventilation [9–10].

There are mixed findings for HTN among COVID-19 patients with mortality. One study reports HTN was positively associated with mortality [11]. However, another study only reports a positive association for mortality when patients had both HTN and diabetes mellitus [12]. There are mixed findings for GIB among COVID-19 patients with mortality. One study reported that one of ten COVID-19 patients with GIB ultimately died with GIB as a contributing cause of death [13]. Furthermore, in-hospital mortality is positively associated with patients who suffer in-hospital cardiac arrests with GIB as a secondary diagnosis [14]. However, another study reported that most COVID-19 patients with GIB responded to conservative management and had a low mortality rate associated with GIB [15].

AKI is positively associated with HTN [16]. There does not appear to be any research on the association of HTN with AKI in COVID-19 patients. Renal dysfunction is a common indicator for a poor outcome of cirrhosis with acute GIB [17]. Although there does not appear to be any research on GIB associated with AKI in COVID-19 patients, there is research on GIB with end stage renal disease (ESRD) in COVID-19 patients. One study found that COVID-19 patients with ESRD were associated with a higher risk of GIB [18].

Patients treated with antihypertensive medications prior to shock onset did not require increased vasopressor doses or duration [19]. As COVID-19 patients are at risk for severe disease, there may be a need for those with HTN to need vasopressors or even mechanical ventilation [11]. There does not appear to be any research regarding HTN with vasopressor use or mechanical ventilation in COVID-19 patients. Furthermore, patients with in-hospital cardiac arrest may be at high risk for GIB since they are often critically ill and most require invasive mechanical ventilation [14].

There are mixed findings on the association of HTN or GIB with mortality in COVID-19 patients but there does not appear to be any research on the combination of both HTN and GIB with mortality in COVID-19 patients. There does not appear to be any research on the association of HTN or GIB with AKI, vasopressor use, and/or mechanical ventilation in COVID-19 patients. Our primary aim is to study the association of HTN and GIB with a composite outcome of mortality, AKI, vasopressor use, and/or mechanical ventilation. Our secondary aims are to study the association of HTN and GIB with each component of the composite outcome. We hypothesize that

HTN and GIB will each be positively associated with mortality, AKI, vasopressor use, and mechanical ventilation. We also hypothesize that the combination of HTN and GIB will be associated with poorer outcomes in COVID-19 patients than with those having either HTN or GIB alone.

Material and Methods

Setting

This is a retrospective study of 2,711 consecutive COVID-19 patients treated from March 2020 through February 2021. The study was conducted in a public hospital in New York City. The inclusion criteria were patients who were 18 years and above that tested positive for COVID-19 with a polymerase chain reaction test. There were no exclusion criteria. The study was ethically conducted, performed in accordance with the Declaration of Helsinki, and received Institutional Review Board approval. A waiver for informed consent was obtained due to the retrospective nature of the study.

Variables

There were four groups consisting of 1) no GIB, no HTN. 2) yes HTN, no GIB. 3) yes GIB, no HTN, and 4) yes GIB, yes HTN. Covariates included age (years), sex (female/male), diabetes, chronic obstructive pulmonary disease (COPD), coronary artery disease (CAD), chronic kidney disease (CKD), and heart failure, all measured as no versus yes. The primary outcome variable was a composite of presence of either mortality, AKI, vasopressor use, and/or mechanical ventilation. Secondary outcome variables were the individual components of the composite variable.

Statistical analyses

Descriptive statistics of mean and standard deviation were used to describe the continuous variable of age and frequency and percentage were used to describe the categorical variables. Analysis of variance compared the GIB-HTN groups to the continuous variable of age. The Pearson chi square test compared the GIB-HTN groups to the categorical variables. Any demographic or medical history variable significantly differing between the GIB-HTN groups was included as a covariate in the multivariate logistic regression analyses for the outcome variables. Alpha level for significance was $p < 0.05$. All analyses were two sided. IBM SPSS Statistics version 28 was used for all analyses (Armonk, New York, 2021).

Results

The GIB-HTN groups consisted of no GIB/no HTN (n = 653), yes HTN/no GIB (n = 1,620), yes GIB/no HTN (n = 104), and yes GIB/yes HTN (n = 334). Table 1 shows the comparisons between the GIB-HTN groups. The demographic variable of age significantly differed where the yes GIB/yes HTN group had the greatest mean age ($p < 0.001$). The medical history variables of diabetes, COPD, CAD, and heart failure each significantly differed (all $p < 0.001$) where the yes GIB/yes HTN group had the greatest percentage. CKD significantly differed ($p < 0.001$) where the yes HTN/no GIB group had the greatest percentage. The outcome variables of composite outcome, mortality, AKI, vasopressor use, and mechanical ventilation use each significantly differed (all $p < 0.001$) where the yes GIB/yes HTN and yes HTN/no GIB groups had the greatest percentages.

Table 1. Comparisons between the groups.

Variable	No GIB No HTN M (SD) or # (%) (n = 653)	Yes HTN No GIB M (SD) or # (%) (n = 1,620)	Yes GIB No HTN M (SD) or # (%) (n = 104)	Yes GIB Yes HTN M (SD) or # (%) (n = 334)	p-value
Demographics					
Age (years) [mean]	48.2 (18.12)	69.6 (16.58)	52.7 (16.37)	71.1 (13.97)	<0.001
Sex (male)	346 (53.0)	875 (54.0)	69 (66.3)	177 (53.0)	0.08
Medical history					
Diabetes (yes)	185 (28.3)	1,027 (63.4)	31 (29.8)	235 (70.4)	<0.001
COPD (yes)	48 (7.4)	290 (17.9)	13 (12.5)	95 (28.4)	<0.001
CAD (yes)	41 (6.3)	555 (34.3)	4 (3.8)	119 (35.6)	<0.001
CKD (yes)	141 (21.6)	536 (33.1)	7 (6.7)	94 (28.1)	<0.001
Heart failure (yes)	27 (4.1)	415 (25.6)	3 (2.9)	89 (26.6)	<0.001
Outcomes					
Composite	169 (25.9)	1,005 (62.0)	34 (32.7)	195 (58.4)	<0.001
Mortality (yes)	87 (13.3)	470 (29.0)	21 (20.2)	101 (30.2)	<0.001
AKI (yes)	99 (15.2)	845 (52.2)	28 (26.9)	169 (50.6)	<0.001
Vasopressor (yes)	85 (13.0)	415 (25.6)	19 (18.3)	89 (26.6)	<0.001
Mechanical ventilation (yes)	78 (11.9)	343 (21.2)	21 (20.2)	86 (25.7)	<0.001

M — mean, SD — standard deviation, GIB — gastrointestinal bleed, HTN — hypertension, COPD — chronic obstructive pulmonary disease, CAD — coronary artery disease, CKD — chronic kidney disease, AKI — acute kidney injury.

Table 2 shows multivariate logistic regression analyses for the composite outcome, mortality, and AKI. In the multivariate logistic regression analysis for the composite outcome of mortality, AKI, vasopressor use, and mechanical ventilation use, the GIB-HTN groups of yes HTN/no GIB (OR:1.47, 95% CI:1.13, 1.89, p <0.001) and yes GIB/no HTN (OR:1.68, 95% CI:1.02, 2.78, p <0.001) were each significantly positively associated with the composite outcome. The yes GIB/yes HTN group was not significantly associated with the composite outcome. Also, increased age, diabetes, COPD, CKD, and heart failure were each significantly positively associated with the composite outcome. In the multivariate logistic regression analysis for mortality, none of the GIB-HTN groups were significantly associated with mortality. Increased age, COPD, and CKD were each significantly positively associated with mortality. In the multivariate logistic regression analysis for AKI, each of the GIB-HTN groups were significantly positively associated with AKI with the yes GIB/no HTN group having the largest odds ratio (OR: 3.34, 95% CI: 1.91, 5.84, p <0.001), while the yes HTN/No GIB group (OR: 2.06, 95% CI: 1.53, 2.78, p <0.001) and the yes GIB/yes HTN group (OR: 1.98, 95% CI: 1.34, 2.93, p <0.001) had similar value odds ratios. Also, increased age, diabetes, CAD, CKD, and heart failure were each significantly positively associated with AKI.

Table 2. Multivariate logistic regression analyses for the composite outcome, mortality, and acute kidney injury.

Variable	Composite OR (95% CI)	p-value	Mortality OR (95% CI)	p-value	AKI OR (95% CI)	p-value
Group						
No GIB, No HTN	1.00		1.00		1.00	
Yes HTN, No GIB	1.47 (1.13, 1.89)	0.003	0.80 (0.59, 1.09)	0.15	2.06 (1.53, 2.78)	<0.001
Yes GIB, No HTN	1.68 (1.02, 2.78)	0.04	1.56 (0.89, 2.76)	0.12	3.34 (1.91, 5.84)	<0.001
Yes GIB, Yes HTN	1.12 (0.79, 1.59)	0.53	0.80 (0.55, 1.17)	0.24	1.98 (1.34, 2.93)	<0.001
Age (years)	1.05 (1.04, 1.06)	<0.001	1.05 (1.04, 1.06)	<0.001	1.05 (1.045, 1.06)	<0.001
Diabetes (yes)	1.64 (1.35, 1.98)	<0.001	1.19 (0.97, 1.47)	0.09	1.47 (1.20, 1.80)	<0.001
COPD (yes)	1.95 (1.50, 2.54)	<0.001	1.82 (1.44, 2.30)	<0.001	1.27 (0.98, 1.66)	0.07
CAD	1.18 (0.93, 1.50)	0.17	0.92 (0.73, 1.15)	0.46	1.42 (1.11, 1.80)	0.01
CKD	9.05 (6.99, 11.71)	<0.001	2.40 (1.94, 2.97)	<0.001	17.76 (13.48, 23.41)	<0.001
Heart failure (yes)	1.81 (1.37, 2.38)	<0.001	1.13 (0.88, 1.43)	0.34	1.47 (1.13, 1.93)	0.01

OR — odds ratio, CI — confidence interval, GIB — gastrointestinal bleed, HTN — hypertension, COPD — chronic obstructive pulmonary disease, CAD — coronary artery disease, CKD — chronic kidney disease, AKI — acute kidney injury. Nagelkerke R Square: Composite: 0.43, Mortality: 0.23, AKI: 0.50.

Table 3 shows multivariate logistic regression analyses for vasopressor use and mechanical ventilation use. In the multivariate logistic regression analysis for vasopressor use, the yes HTN/no GIB group approached significance for a positive association (OR: 1.34, 95% CI: 1.00, 1.81, p = 0.05). Increased age, diabetes, COPD, and CKD were each significantly positively associated with vasopressor use. In the multivariate logistic regression analysis for mechanical ventilation use, the yes GIB/no HTN group was significantly positively associated with mechanical ventilation use (OR: 1.85, 95% CI: 1.07, 3.20, p = 0.03). Also, diabetes, COPD, and CKD were each significantly positively associated with mechanical ventilation use.

Table 3. Multivariate logistic regression analyses for vasopressor and mechanical ventilation.

Variable	Vasopressor OR (95% CI)	p-value	Ventilation OR (95% CI)	p-value
Group				
No GIB, No HTN	1.00		1.00	
Yes HTN, No GIB	1.34 (1.00, 1.81)	0.05	1.26 (0.93, 1.72)	0.14
Yes GIB, No HTN	1.50 (0.86, 2.61)	0.16	1.85 (1.07, 3.20)	0.03
Yes GIB, Yes HTN	1.26 (0.86, 1.83)	0.23	1.44 (0.98, 2.12)	0.06
Age (years)	1.01 (1.002, 1.014)	0.01	1.01 (1.00, 1.01)	0.15
Diabetes (yes)	1.47 (1.20, 1.80)	<0.001	1.64 (1.32, 2.04)	<0.001
COPD (yes)	2.51 (2.00, 3.14)	<0.001	2.73 (2.16, 3.44)	<0.001
CAD	1.16 (0.92, 1.45)	0.21	0.89 (0.69, 1.13)	0.32
CKD	1.69 (1.38, 2.08)	<0.001	1.49 (1.20, 1.85)	<0.001
Heart failure (yes)	1.14 (0.90, 1.46)	0.29	1.25 (0.97, 1.61)	0.09

OR — odds ratio, CI — confidence interval, GIB — gastrointestinal bleed, HTN — hypertension, COPD — chronic obstructive pulmonary disease, CAD — coronary artery disease, CKD — chronic kidney disease. Nagelkerke R Square: vasopressor: 0.11, mechanical ventilation: 0.09.

Discussion

We found that the yes HTN/no GIB and yes GIB/no HTN groups were each significantly associated with increased odds for the composite outcome of mortality, AKI, vasopressor use, and mechanical ventilation use. All three groups of yes HTN/no GIB, yes GIB/no HTN, and yes GIB/yes HTN were each significantly associated with increased odds for AKI. The yes HTN/no GIB group approached significance for increased odds for vasopressor use. The yes GIB/no HTN group was significantly associated with increased odds for mechanical ventilation use. None of the GIB/HTN groups were significantly associated with mortality.

We found that the presence of either HTN or GIB was significantly associated with increased odds for the composite outcome while the presence of both HTN and GIB combined was protective and not significantly associated with the composite outcome. We are unaware of any previous research on the presence of both HTN or GIB and their association with the components of our composite outcome among COVID-19 patients. A study with the respiratory viral disease of influenza found that patients with both HTN and GIB had higher associations for mortality than those with either HTN or GIB alone [20]. Our finding for COVID-19 differs from this study. We speculate that HTN was a protective factor for GIB in COVID-19 patients. As patients become hypotensive and develop GIB, their blood pressure will quickly drop. We believe that those with HTN were able to maintain adequate blood pressure to allow vasoconstriction and shunt off blood to prevent damage to vital organs.

In our study, the presence of either HTN or GIB or the combination of both HTN and GIB was not associated with mortality. Previous research with COVID-19 patients shows mixed findings of HTN and/or GIB with regard to mortality with some reporting a positive association while others report either a negative association or an association only for certain patient subgroups [11–13, 15]. Our study is similar to the research showing no association. In general, the presence of HTN and GIB inflict harm including mortality with COVID-19 patients that leads to many illnesses [21]. We speculate that our sample with COVID-19 patients had two broad categories of patients; those admitted for COVID-19 and those admitted for another disease that upon testing were diagnosed with COVID-19. It is possible that those admitted for the other disease may not have as much mortality as would be expected with COVID-19 and therefore we did not see any association with mortality.

We found that all three groups of yes HTN/no GIB, yes GIB/no HTN, and yes GIB/yes HTN were each significantly associated with increased odds for AKI. The SARS-CoV-2 nucleocapsid protein indicative of COVID-19 is observed in tubular structures in the kidneys and there is the presence of COVID-19 virus-like particles in podocytes and renal tubular epithelial cells [22–23]. This suggests that COVID-19 could directly infect human kidney tubules and induce cytoplasmic renal tubular inclusions. It is known for AKI that HTN and GIB cause AKI because of the hemodynamic or hemostatic changes in the body. We suggest that AKI also wreaks havoc in COVID-19 patients as the virus itself may be replicating inside of the kidney parenchyma leading to acute renal failure.

We found that the yes HTN/no GIB group approached significance for increased odds for vasopressor use. The opposite pattern occurred for mechanical ventilation use where the yes GIB/no HTN group was significantly associated with increased odds for mechanical ventilation use. We are not aware of any literature on the association of either HTN or GIB with vasopressor use or mechanical ventilation use with COVID-19 patients. Previous research reports show the initiation of vasopressor is still deba-

table [24]. Most clinicians prefer the use of vasopressors only when blood pressure cannot be maintained despite initial fluid expansion. Nevertheless, we suggest that the initiation of vasopressor therapy in the early stages of hemorrhagic shock may have usefulness in restoring hemodynamic parameters and vital organ perfusion. Mechanical ventilation is a known risk factor for GIB [25]. We suggest that this is the reason for the association of GIB with mechanical ventilation.

A strength of this study is the comprehensive approach for understanding HTN and GIB in COVID 19 patients. This study has several limitations. First, the yes GIB/no HTN group had a relatively smaller sample size as compared to the other groups which may have resulted in non-significance for certain analyses. Second, GIB may not be a universal concept but rather is influenced by medications and preexisting conditions. We lacked clinical information that could further inform the underlying risk of GIB such as use of aspirin and antiplatelet agents, warfarin, heparin, and other anticoagulant agents. Similarly, information regarding pre-existing hepatic and renal dysfunction or conditions predisposing to coagulopathy or bleeding was limited. Future research should study the association of these four HTN/GIB groups with number of hospitalization days and number of days with intensive unit care.

Conclusions

In conclusion, we found that HTN or GIB alone were each significantly associated with increased odds for the composite outcome of mortality, AKI, vasopressor use, and mechanical ventilation use while having both HTN and GIB was protective and not significantly associated with the composite outcome. We recommend that clinicians be aware of such findings when treating patients with COVID-19 as those with both HTN and GIB may not need as aggressive treatment as compared to those with either HTN and GIB alone. By maintaining blood pressure or even having an elevated blood pressure, COVID-19 patients with GIB can still perfuse their vital organs and therefore decrease the risk of adverse events or need for aggressive treatment.

Author Contribution Statement

I.B.: study design, data interpretation, drafting manuscript, final approval of manuscript
J.F.: study design, data analysis, data interpretation, critically revising manuscript for important intellectual content, final approval of manuscript
A.D.: study design, data acquisition, data interpretation, critically revising manuscript for important intellectual content, final approval of manuscript
J.W.: study design, data acquisition, data interpretation, critically revising manuscript for important intellectual content, final approval of manuscript

J.T.: study design, data acquisition, data interpretation, critically revising manuscript for important intellectual content, final approval of manuscript

All authors accept responsibility for the paper as published.

Funding

None declared.

Conflict of interest

The authors do not have any financial or competing interests.

Abbreviations

AKI — acute kidney injury
CAD — coronary artery disease
CKD — chronic kidney disease
COPD — chronic obstructive pulmonary disease
ESRD — end stage renal disease
GIB — gastrointestinal bleed
HTN — hypertension

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