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Systematic Review

Increased Overall Mortality in Patients Admitted for Gastrointestinal Bleeding and COVID-19 Infection Compared to No COVID-19 Infection: A Systematic Review and Meta-Analysis

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Abstract

(1) Background: Patients admitted for gastrointestinal bleeding (GIB) who are diagnosed with COVID-19 at presentation may face significant therapeutic challenges. The delicate balance between the use of anticoagulant and anti-inflammatory therapy to address COVID-19 and hemostasis targets can, in turn, lead to delays in COVID-19 treatment until bleeding is controlled. The published systematic reviews and meta-analyses that were reviewed included patients with both GIB and COVID-19 regardless of GIB presence at admission, and a separate analysis of patients admitted for GIB and tested for COVID-19 infection during hospitalization was not performed. (2) Methods: PubMed, Web of Science, and Scopus databases were used to access articles published from 1 December 2019 to 20 December 2024. Retrospective studies involving human subjects with GIB and COVID-19 were included in the final analysis. The exclusion criteria were as follows: pediatric population studies; the absence of a GIB control group; reviews, conference abstracts, expert opinions, and letters.The risk of bias in the included studies was assessed using the rank correlation test and Begg's and Egger's regression tests. We estimated the outcomes using the pooled odds ratio (OR) and the 95% confidence interval (95% CI). (3) Results: Seven studies, which included 3291 patients admitted for GIB who tested positive for COVID-19 infection, were included in our systematic review; four studies with a control group of patients with GIB but without COVID-19 infection were included in our meta-analysis. The odds of mortality among COVID-19-infected patients admitted for GIB were 3.80. There was heterogeneity regarding the site of GIB (some studies included all forms of GIB, others included only UGIB) and the study period (most studies included only patients from the first pandemic wave, and only one study reported cases from the first 2 years of the pandemic, including the delta pandemic wave). (4) Conclusions: COVID-19 infection in patients admitted for GIB was associated with a higher overall mortality rate.

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1. Introduction

The COVID-19 virus has led to a global pandemic which began in late 2019 and spring 2020 [1–8], with more than 600 million cases reported from 2019 to 2023 [9]; however, the severity of cases has decreased significantly since the appearance of the omicron variant of the virus [10]. The main manifestations include fever, fatigue, and dry cough, progressing to dyspnea and ARDS within 6–8 days of exposure [2,11]. Gastrointestinal symptoms are noted in 3–40.7% of patients [4,12], sometimes at onset and accompanied by the absence of respiratory symptoms in up to 2% of COVID-19 patients [7]. Most gastrointestinal symptoms in COVID-19 patients include nausea/vomiting, a loss of appetite, diarrhea, abdominal pain, and rarely, gastrointestinal bleeding [2,6,7,13,14]. In a meta-analysis, 20.3% of COVID-19 patients had GI symptoms (higher in European studies) and 26.7% had persistent viral shedding for 19.2 days on average [4]. The overall mortality rate was 1.5–3.6% during the first pandemic wave; underlying comorbidities may have increased the mortality rates [11].

Acute gastrointestinal bleeding (GIB) constitutes a major emergency, with an estimated overall mortality of 2–10% [15,16]. The mortality rate is higher in upper GIB (UGIB) than in lower GIB (LGIB), and in the case of variceal bleeding, up to 20% of patients can die [15]. Mortality is usually correlated with the severity of bleeding and associated comorbidities in the case of non-variceal bleeding [17,18], and with liver failure in the case of variceal bleeding. Most deaths in patients with GIB are not related directly to exsanguination, rather to poorly tolerated blood loss, aspiration, advanced age, and the presence of severe comorbidities [15,17,18]. Elderly patients and those with severe cardiopulmonary, liver, oncological, or renal diseases have a higher overall mortality risk when gastrointestinal bleeding is present [17,18], and such factors are included in several risk scores (Rockall, Baylor, AIMS65, ABC) for patients with UGIB [19].

Endoscopic hemostasis is the cornerstone of treatment, especially in UGIB [15], and it should be performed as early as possible after stabilization. Upper digestive endoscopy is a procedure with aerosolization risk and therefore carries a higher risk of COVID-19 contamination [1,3,20,21]. Precautions regarding risk management impact the timing and efficiency of endoscopic procedures; the need for COVID-19 testing and isolation also negatively influences the timing of endoscopy and potentially increases overall mortality. Moreover, pneumonia and intubation as a result of COVID-19 infection can complicate upper digestive endoscopy procedures [1].

The COVID-19 pandemic has had multiple negative consequences on healthcare systems because of lockdown measures; the need for dedicated beds, personnel, and circuits for COVID-19 patients; insufficient capabilities in response to emergent cases; and the effect of patients' fear of hospital admissions [21]. The association between GIB and COVID-19 infection can, in many cases, be difficult to be manage due to the risk of extensive thrombosis and the need for anticoagulant therapy, especially in severe COVID-19 infections and in hospitalized COVID-19 patients, which represents a major risk factor for bleeding [1].

GIB is present in up to 13% of COVID-19 infections [2,13,16]; in a recent meta-analysis, the incidence rate of GIB in 33 included studies was 0.47–19% [1]. There are two situations in which GIB and COVID-19 an concurrently be present: in patients admitted because of GIB, who tested positive for COVID-19 on admission or during hospitalization (which may

have a significant impact on mortality, because of the delay in both endoscopy and anticoagulant therapy and the need for stabilization), and GIB appearing during hospitalization for COVID-19 infection, when systemic stress (especially in ICU-admitted cases), hypoxemia, therapy (anticoagulants, anti-inflammatory drugs), and rarely the direct cytopathic effect of the virus may induce GIB. COVID-19 patients harbor a high risk of thrombotic complications [1–3], and most symptomatic COVID-19 cases need prophylactic or therapeutic anticoagulants [2]. The presence of GIB at admission may significantly delay the onset of anticoagulant treatment, thus impacting the overall mortality risk in patients with both GIB and COVID-19 infection. Delayed endoscopy because of COVID-19 infection can also be associated with a higher overall mortality rate, whereas studies in patients with GIB and no endoscopy performed have shown higher overall mortality compared to cases with both variceal and non-variceal bleeding [19]; because of contamination risk, most endoscopy centers have favored a "wait and see" approach in patients with upper GIB and COVID-19 infection, with endoscopy employed in cases with no response to conservative management within 24 h (hemodynamic instability, Hb level decrease despite blood replacement) [16].

Our systematic review and meta-analysis aimed to assess the impact of COVID-19 on the overall mortality rate, rebleeding rate, and rates of diagnostic and therapeutic endoscopy in patients admitted for GIB. Because currently available meta-analyses included patients with both GIB and COVID-19 infection, regardless of whether GIB was the main reason for admission [1–5,7,16,22], we intend to analyze whether the presence of COVID-19 infection in patients admitted for GIB is associated with a higher overall mortality and rebleeding rate, and with a lower rate of diagnostic or therapeutic endoscopy.

2. Materials and Methods

2.1. Search Strategies

A literature review was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [23]. The PROSPERO registration number, including the review protocol, is CRD42024567821. The results of the review are reported using the PRISMA 2020 checklist (Table S1).

A literature search was performed using PubMed, Web of Science, and Scopus databases. The last search was made on 1 December 2024, with another run before the final analysis for any further identified studies. An initial search in PubMed was made to identify relevant keywords and synonyms for GIB and COVID-19 infection used in the literature; the Medical Subject Headings terms (MeSH terms) identified were "gastrointestinal bleeding", "gastrointestinal hemorrhage", "COVID-19", "SARS-CoV-2", and "COVID-2019." In the next step, an extensive literature search was performed using the previously described terms combined with Boolean Operators ("AND" and "OR") as follows: (("gastrointestinal bleeding") OR ("gastrointestinal hemorrhage")) AND (("COVID-19") OR ("SARS-CoV-2") OR ("COVID-2019")). Published retrospective articles that fully complied with the following inclusion criteria were deemed eligible: (1) published in English, (2) studies involving human subjects with GIB and COVID-19 infection, and (3) admissions because of GIB. The exclusion criteria were as follows: the inclusion of the pediatric population; the absence of a GIB control group; a lack of data regarding GIB as the main admission criteria; reviews, conference abstracts, expert opinions, and letters. Case series were not included in the statistical analysis but are mentioned in the Results section (Figure 1).

Both the abstract and full-text publications were reviewed. In the last step, the reference lists for the articles selected during the initial step were also screened for relevant articles that may have been missed.

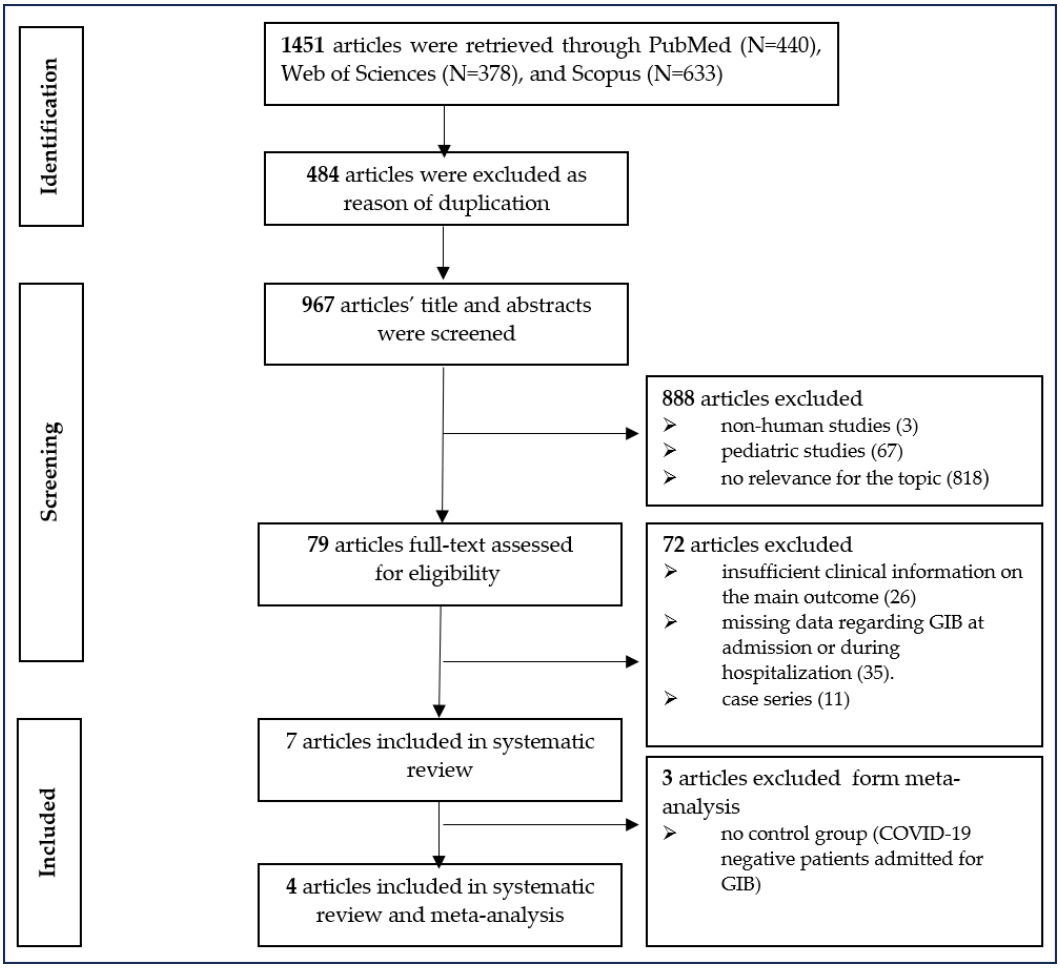


Figure 1. PRISMA flow chart of literature search and study selection process.

2.2. Outcome Variables and Data Extraction

Two independent reviewers (SM.C and CM.M) performed the selection process and read the selected publications. In cases of disagreement, a third reviewer (I. R.) decided to include or exclude a publication.

We assessed the methodological quality of the included studies using the Cochrane Risk of Bias Tool (RoB2) [24]. This tool evaluates seven key domains: random sequence generation (selection bias); allocation concealment (selection bias); the blinding of participants/personnel (performance bias); the blinding of outcome assessors (detection bias); incomplete outcome data (attrition bias); selective reporting (reporting bias), and other potential biases (e.g., confounding factors). Each domain was rated as "low risk", "high risk", or "unclear risk" based on the study methodology. Two reviewers (SM.C and I.R) were involved in the quality assessment, and a third reviewer (A.TS.) was involved in cases of disagreement.

The extracted basic information included the first author, the year of publication, the publication country, the data range of the patient selection, the sample size, and patient characteristics (age, sex, cirrhosis, endoscopy, therapeutic endoscopy, and rebleeding). The main outcome was the overall mortality rate (in-hospital or at 30 days). The secondary outcomes were the rebleeding rate and diagnostic and therapeutic endoscopy.

2.3. Statistical Analysis

The data collected from selected papers were used for the overall mortality rate assessment of patients with GIB and COVID-19 infection compared with patients with

GIB and without COVID-19 infection. Extracted data were computed using an Excel spreadsheet. The log OR, along with the 95% confidence interval and *p*-value for the overall mortality in COVID-19-positive patients with GIB as opposed to COVID-19-negative patients, was assessed. Confounding factors, including the GIB site (upper versus lower GIB), UGIB etiology (variceal UGIB, non-variceal UGIB), age, sex, comorbidities, UGIB bleeding scores (GBS, Rockall score), whether endoscopy was performed (yes versus no), and whether therapeutic endoscopy was performed (yes versus no), were included in the analysis. Heterogeneity between studies was assessed using I2 statistics and the Q-test. Low, moderate, and high heterogeneities were considered at 25%, 50%, and 75%, respectively [24]. Heterogeneity (tau2) was estimated using the maximum-likelihood estimator. In the case of heterogeneity (tau2 > 0), a prediction interval of the true outcomes was also provided. A random-effect meta-analysis model was also used in case of heterogeneity of the studies; otherwise, a fixed-effect meta-analysis model was fitted to the data. Publication bias was evaluated using a funnel plot. The rank correlation Begg's and Egger's regression tests (using the standard error of the observed outcomes as predictors) were also used to verify funnel plot asymmetry and publication bias. Statistical analysis was conducted in RevMan (version 7.2.0, The Cochrane Collaboration, 2024) and R with the metafor package [25]. Due to the limited number of studies, we did not apply the DerSimonian and Laird random-effects method in RevMan, as it is known to exhibit poor statistical performance in meta-analyses with few studies. Instead, we addressed this issue by using the new random-effects methods introduced by Cochrane in 2024.

3. Results

3.1. Characteristics of the Included Studies

A total of 1451 studies were retrieved from the PubMed, Web of Science, and Scopus databases. A total of 484 articles were excluded because of duplication. After title and abstract screening, 888 articles were excluded because they were non-human or pediatric. The full texts of the 79 remaining articles were assessed, and 72 articles were removed because they did not report the outcome of interest.

Seven studies were included in this review, with 3291 patients with GIB [20,21,26–30]. A total of 3263 cases had UGIB, 10 had LGIB, and 18 had unspecified GIB. One population-based study included only non-variceal UGIB from the USA [30], one included both UGIB and LGIB [20], and five studies from tertiary care centers included UGIB (both variceal and non-variceal). A total of 23 cases had variceal bleeding, 3192 had non-variceal bleeding, and the type of UGIB was not stated in 76 cases. Four studies analyzed the main outcomes of GIB without COVID-19 infection as the control group [21,28–30], two studies had COVID-19 patients without GIB as the control group [20,27], and one study had no control group [26]. In all of the studies, the overall mortality rate was assessed; data regarding the bleeding-related cause of death were available in five studies [20,21,27–29]. The overall mortality rate was 5–59% for all GIB, 5–59% for UGIB, and 20% for LGIB (Table 1); in the five studies detailing the cause of death, the direct attributable bleeding-related mortality in GIB patients with COVID-19 infection was 2.1% (3/145 patients), as seen in Table S1. Except for the study that included only NVUGIB, the overall mortality rate in UGIB was between 13 and 59%. Several case reports or case series with GIB on admission were also published; 10 patients with GIB on admission were described; five had UGIB and five had LGIB, with an overall mortality rate of 5/10 (50%) -2/5 in UGIB and 3/5 in LGIB [31–33].

Table 1. Studies included in the systematic review and meta-analysis.

Author, Year, Country	Study Period (Publication Year)	Patients Bleeding Type	Control Group	Gender (%Males)	Age (Mean ± Stdev)	Endoscopy No (%)	Therapeutic Endoscopy (%)	Mortality	Rebleeding
Martin 2020 USA [20]	4 March–23 April 2020, (2020)	41 (31 UGIB, 10 LGIB)	COVID-19 without GIB	27 (66%) vs. 54 (66%)	68.7 (15.1) vs. 67.6 (14.3)	10/31 (32%) UGIB 5/10 (50%) LGIB	40	8 (26% UGIB), 2 (20% LGIB)	4 (13%) UGIB 1 (10%) LGIB
Cazacu 2023, Romania [21]	March 2020–December 2021, (2023)	39 UGIB	459 UGIB without COVID-19	22/39 (56.4%) vs. 312/459 (68%)	67.8 (12.65) vs. 63.1 (14.60)	17/39 (43.6%) vs. 384/459 (83.7%)	23.5 vs. 24	23 (59%) vs. 13.7%	1 (2.6%) vs. 44 (7.8%)
Shalimar 2021, India [26]	22 April–22 July 2020, (2021)	24 UGIB	No control group	17/24 (70.8%)	45.8 (12.7)	4% (1/24)	100	3 (13%)	2 (8.7%)
Rosevics 2021 Brasil [27]	March–August 2020, (2021)	9 UGIB	COVID-19 without GIB	5/9 (55.6) vs. 296/539 (54.9%)	58 (10.2) vs. 57 (15.1)	100% (9/9)	20	4 (44.4%)	-
Iqbal 2022, USA [28]	March 2020–February 2021, (2022)	18 GIB	54 GIB without COVID-19	12 (66.7) vs. 36 (66.7)	68.8 (13.31) vs. 70.0 (11.29)	6/18 (33.3%) vs. 40/54 (74.1%)	22.2 vs. 25.9	7 (38.9%) vs. 18.5%	3 (16.7%) vs. 6 (11.3%)
Smith 2022, USA [29]	January 2020–March 2021, (2022)	5 UGIB	171 UGIB without COVID-19	NA	NA	2/5 (40%) vs. 171/171 (100%)	100	2 (40%) vs. 20.47%	1 (20%)
Elfert 2023, USA [30]	January–December 2020, (2024)	3155 UGIB Non-variceal	229790 NVUGIB without COVID-19	1700 (54%) vs. 126575 (55%)	67.4 (15) vs. 66.2 (15)	39% vs. 49%	21 vs. 28	158 (5%) vs. 2%	-

UGIB = upper gastrointestinal bleeding, LGIB = lower gastrointestinal bleeding, GIB = gastrointestinal bleeding.

Except for the risk of selection bias due to the retrospective design of all studies, we observed a low risk of bias across all six fields for all studies (Figure 2).

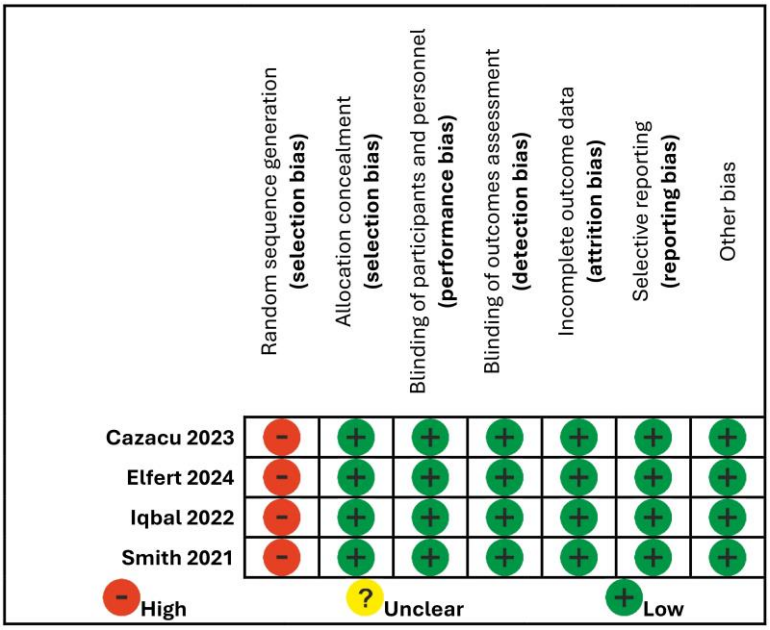


Figure 2. A summary of the risk of bias [21,28–30].

3.2. The Impact of COVID-19 on the Overall Mortality of Patients with GIB

Four studies had patients with GIB without COVID-19 infection as a control group and were included in the meta-analysis: Cazacu et al. [21], Iqbal et al. [28], Smith et al. [29], and Elfert et al. [30]. COVID-19-positive patients with GIB had a much higher overall mortality rate compared to those who were COVID-19-negative with GIB (3.80 overall mortality OR, 95% CI 1.76–8.19), ranging from 2.58 to 9.04, with all estimates (100%) being positive (Figure 3A). The overall mortality was higher in all studies but heterogeneous (Q(3) = 11.98, p = 0.0076, tau2 = 0.40, I2 = 75%); the estimated average log OR based on the RE model was 1.33 (95% CI: 0.72–1.94, z = 3.40, p = 0.0007). One study [21] may be a potential outlier in the context of this model (residual values larger than ±2.5). No study was deemed to be overly influential; rank correlation and regression tests indicated no funnel plot asymmetry (p = 1.0 and p = 0.84, respectively)—Figure 3B.

3.3. The Association Between Age and COVID-19 Positivity

The mean age of patients admitted for GIB was estimated for COVID-19-positive and COVID-19-negative cases; three studies (3212 patients with COVID-19 and 230,293 patients without COVID-19) were included in the analysis. We found a small but statistically significant age difference between COVID-19-positive and COVID-19-negative patients admitted for GIB (z = 4.66, p < 0.00001), with COVID-19 patients being slightly older (mean difference = 1.24; 95% CI 0.72–1.76). The small observed age difference is unlikely to have a significant impact on the mortality difference between COVID-19-positive and COVID-19-negative patients with GIB. The observed standardized mean differences ranged from −1.20 to 4.70, with the main estimates being positive (67%)—Figure 4A. No significant heterogeneity was detected (Q(2) = 3.13, p = 0.21, tau2 = 0.0038, I2 = 36%). Neither the rank correlation nor the regression test indicated any funnel plot asymmetry (p = 1.0 and p = 0.92, respectively), as seen in Figure 4B.

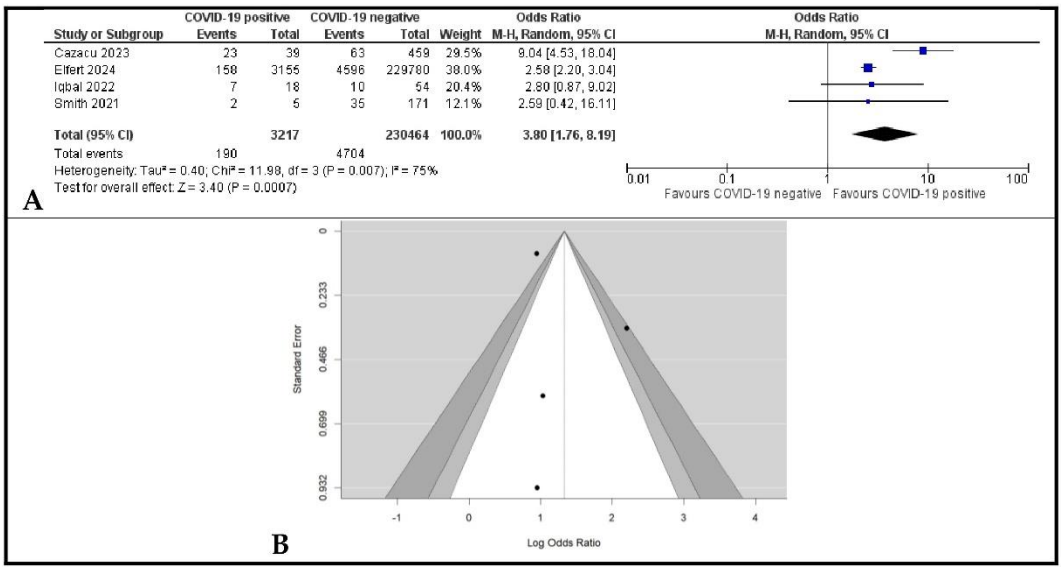


Figure 3. (**A**) The pooled OR of overall mortality among GIB in COVID-19-positive versus COVID-19-negative patients. The effect size points for every study are designed as blue squares with horizontal lines indicating the 95% CI. The pooled outcome is designed as a black diamond with a 95% CI under a random-effect model. (**B**) A funnel plot of the primary included studies estimating the impact of COVID-19 infection on overall mortality among patients admitted for GIB. Each black dot represents an individual study. The x-axis shows the log odds ratio; the y-axis is the standard error (precision). The inverted funnel shape represents the expected distribution of study results in the absence of publication bias. The symmetry of dots around the vertical line (mean effect) suggests minimal publication bias; asymmetry may indicate potential bias. [21,28–30].

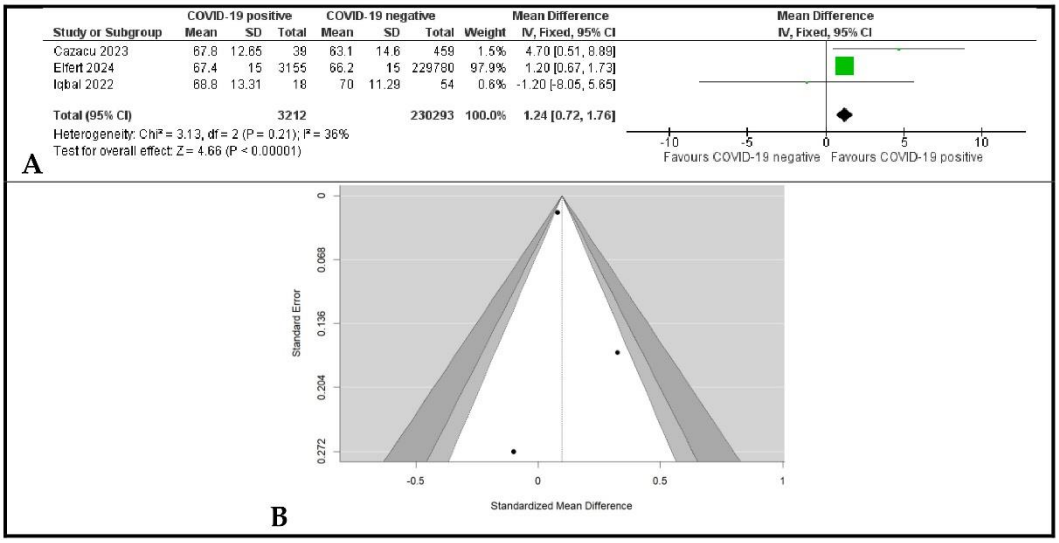


Figure 4. (**A**) The pooled age of GIB patients among COVID-19-positive and COVID-19-negative patients. (**B**) A funnel plot of primary included studies estimating the association between age and COVID-19 infection in GIB-admitted patients. [21,28,30].

3.4. The Impact of COVID-19 Positivity on Rebleeding in Patients with GIB

Three studies (62 patients with COVID-19 and 684 patients without COVID-19) were included in the analysis. The pooled rebleeding rate was 9.4%. No statistically significant difference in the rebleeding risk between COVID-19-positive and negative GIB patients was found (p = 0.36 for overall effect), despite an estimated average OR of 0.60 (95% CI ranged between 0.2 and 1.78); this may be due to the limited sample sizes, particularly for

COVID-19-positive rebleeding events. Low heterogeneity was noted for the rebleeding rate (Q(2) = 0.90, p = 0.64, tau2 = 0, I2 = 0), indicating consistency in direction/effect size across studies, though small study numbers limit robustness—Figure 5A. Neither the rank correlation nor the regression test indicated funnel plot asymmetry (p = 1 and p = 0.7571, respectively), as seen in Figure 5B.

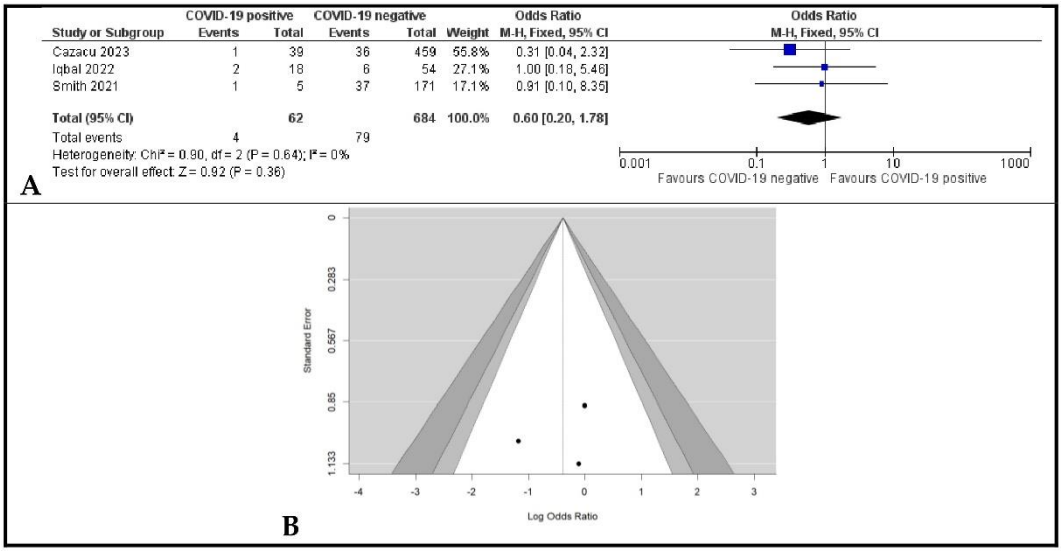


Figure 5. (**A**) A forest plot and (**B**) a funnel plot of the primary included studies estimating the association between rebleeding and COVID-19 infection among GIB patients. [21,28,30].

3.5. The Impact of COVID-19 Positivity on the Rate of Diagnostic Upper Digestive Endoscopy in Patients with GIB

Three studies were included to estimate the pooled impact of COVID-19 positivity on diagnostic upper digestive endoscopy in patients with GIB. The odds of upper digestive endoscopy in the first 24 h after admission were 0.29 among COVID-19-positive patients compared to those among those negative (95%CI 0.08–1.08), as seen in Figure 6A. The rate of digestive endoscopy suggests heterogeneity between studies (Q(2) = 28.52, p < 0.00001, tau2 = 1.21, I2 = 93%), and a random-effects model was fitted to the data. The regression test indicated funnel plot asymmetry (p < 0.0001) but not the rank correlation test (p = 1.0), as seen in Figure 6B.

3.6. The Impact of COVID-19 Positivity on Therapeutic Upper Digestive Endoscopy in Patients with GIB

Three studies reported the number of patients who needed therapeutic upper digestive endoscopy: 670 with UGIB and COVID-19 infection and 64,444 patients with UGIB without COVID-19, as seen in Figure 7A. The estimated average OR based on the fixed-effects model was 0.68 (95% CI 0.63–0.75, p < 0.00001). No significant heterogeneity was detected regarding the need for endoscopic intervention (Q(2) = 0.45, p = 0.80, I2 = 0%). Neither the rank correlation nor the regression test indicated any funnel plot asymmetry (p = 1.0 and p = 0.6818, respectively), as seen in Figure 7B.

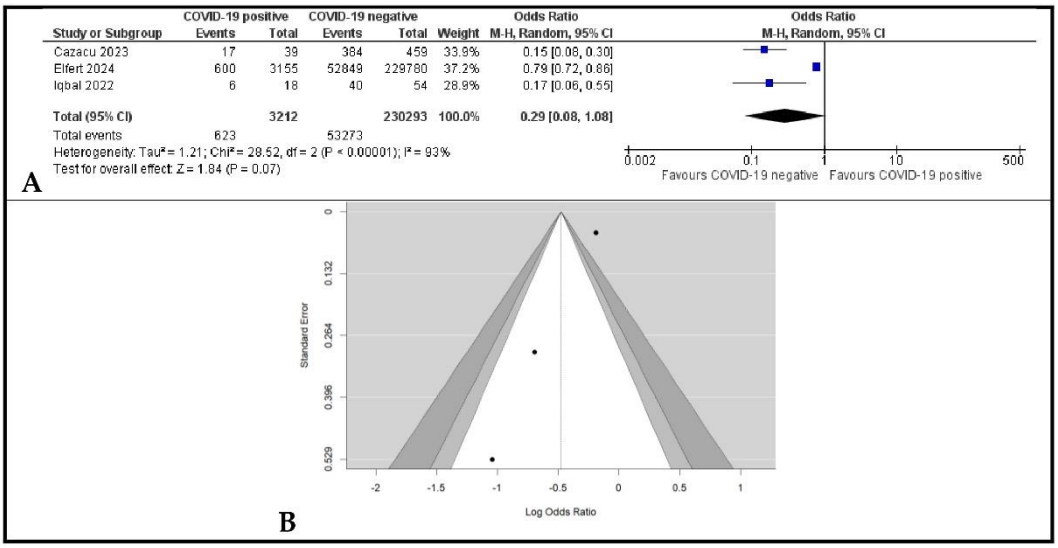


Figure 6. (**A**) A forest plot of the effect of COVID-19 positivity on diagnostic upper digestive endoscopy during the first 24 h after admission in patients with GIB. (**B**) A funnel plot for publication bias assessment of the primary included studies estimating the impact of COVID-19 positivity on diagnostic upper digestive endoscopy among GIB patients. [21,28,30].

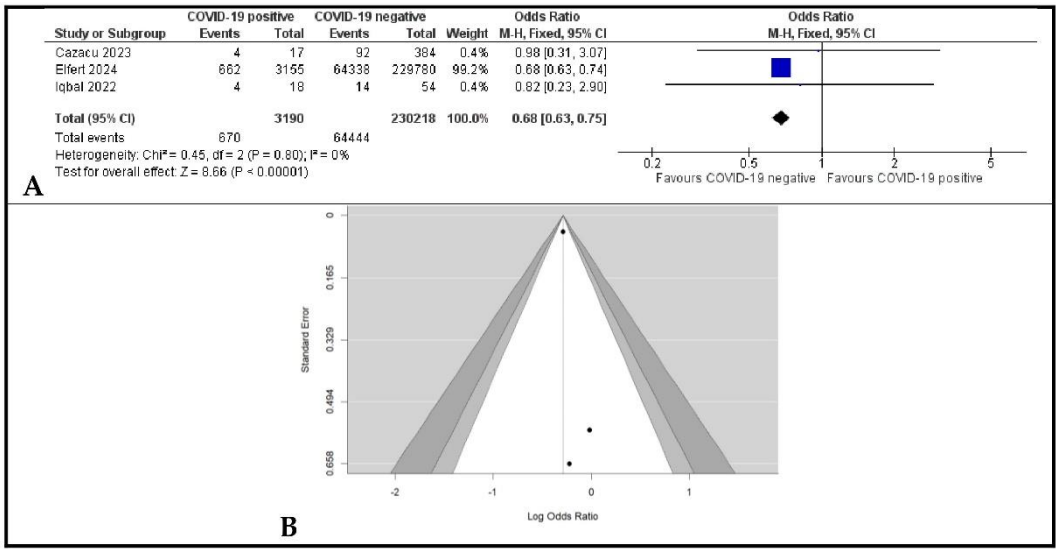


Figure 7. (**A**) A forest plot of the effect of COVID-19 positivity on therapeutic upper digestive endoscopy in patients with GIB. (**B**) A funnel plot for publication bias assessment of the primary included studies estimating the impact of COVID-19 positivity on therapeutic upper digestive endoscopy among GIB patients. [21,28,30].

4. Discussion

The association between GIB and COVID-19 infection may appear in two situations. The first possibility is represented by the onset of GIB in patients already diagnosed with COVID-19, with specific treatment for infection, and more often in hospitalized patients. The second situation refers to the patients who presented with GIB and were diagnosed during admission with COVID-19 infection. Most studies have focused on the first situation of bleeding that appears during hospitalization for COVID-19 infection, with multiple possible mechanisms: the cytopathic effect of the virus favored by a high presence of gut ACE receptors, hypoxemia, sepsis, intravascular disseminated coagulation, increased stress in severe cases, and treatment with NSAID and anticoagulants [1,2,8,13,16,34–39]. The

rates of GIB appearing during hospitalization for COVID-19 infection were estimated to be 0.4–13% [20,40]; gastric ulcerations and peptic ulcers in COVID-19-positive patients represented the main causes of bleeding [41,42], and the severity of COVID-19 infection was associated with a higher risk of GIB [40].

The second situation, in which patients were admitted for GIB and diagnosed with COVID-19 infection during admission, was not properly analyzed in any meta-analyses to date and may pose significant therapeutic problems because of the delicate balance between the need for anticoagulant and anti-inflammatory therapy for COVID-19 infection; the need to meet hemostasis targets can delay COVID-19 therapy until the bleeding has stopped [21]. The waiting time for endoscopy until COVID-19 test results were available and the need for patient isolation, triage, and protective equipment led to a decrease in emergency endoscopy rates for GIB during the pandemic and an increase in the time to endoscopy, often above 24 h, with a possible increase in overall mortality. Several factors related to the delayed presentation of these patients may also contribute to the poor prognosis because, during the pandemic period, most patients were reluctant to visit the hospital until severe manifestations occurred, and patients with less severe cases may have skipped medical consultation and opted for therapy at home.

Increased overall mortality rates have been noted in association with GIB during the pandemic period as compared with 2019, with an 11.1% higher overall mortality in 2020 for NVUGIB, despite similar endoscopic interventions and similar shock presence at admission [43], a 13% higher overall mortality in UGIB, with unadjusted mortality rates of 2.25% in 2020 and 1.99% in 2019 ($p < 0.001$) [44], and 24.8% excess mortality for all GIB in 2020–2022 as compared to 2019 [45]. In most studies, the number of presentations with UGIB was lower during the pandemic [21,22,44,46–48]; the proportion of patients requiring transfusions and with critical Hb levels was higher in one study [49] and similar in another study [50].

A significant number of studies showed high rates of overall mortality in GIB patients with COVID-19 infection during the pandemic period but with marked heterogeneity due to the type of bleeding (UGIB, LGIB, or all types; variceal or non-variceal), and most studies did not differentiate between GIB at admission or during hospitalization. Several case reports or case series, including 13 UGIBs that appeared during hospitalization for COVID-19 infection, showed a 38.5% overall mortality rate [51–57]. Several studies in the USA reported overall mortality rates of 13–43.2% in COVID-19 patients with GIB [58–66]. However, some studies observed no overall mortality difference between patients with GIB and COVID-19 infection and those with GIB and no infection (OR = 0.62, $p = 0.170$) [67]. Several studies from other countries showed overall mortality rates of 69.1% in Kuwait [68], 37.8% in Turkey [69], 39.5% in Thailand [70], 46.4% in Vietnam [71], 36.2% in Iran [72], 52.3% in Malaysia [73], and 21.7% in Northern Italy [74]. The presence of COVID-19 infection in patients with GIB was associated with an OR for overall mortality of 2.05 in a study in Spain [75], 2.26 in a study in Vietnam [71], and 13.7 in a study in China [65].

Several reviews and meta-analyses analyzing overall mortality rates in COVID-19-infected patients are also available [1–3,5,8,22,43], with pooled overall mortality rates of 14.95% [1], 19.1% [3], 25.4% [8], and 29% [22]; the pooled risk of rebleeding was 11.3% [3]. However, all currently available systematic reviews and meta-analyses did not perform a separate analysis of patients admitted for GIB, and a conclusion regarding mortality and rebleeding risk in patients who were COVID-19-positive and admitted for bleeding is not available. A review published in September 2021 analyzed 21 studies that included 123 patients in the final analysis; diagnostic endoscopy was performed in only 40% of cases, endoscopic interventions were needed in 12.2%, and bleeding-related mortality was 1.6% [5]. In most studies, more deaths were related to COVID-19 complications than

to continued bleeding [5,21,64,72]. In our review and meta-analysis, the odds of overall mortality among COVID-19-infected patients with GIB compared with COVID-19-negative patients with GIB were 3.80 (95% CI 1.76–8.19). Although there was some heterogeneity, the true outcomes of the studies were generally similar to the estimated average outcomes. No clear conclusion was made regarding the overall mortality in COVID-19-infected patients with variceal bleeding because only 23 cases of variceal bleeding were included in the meta-analysis. However, a higher overall mortality rate was noted in patients with non-variceal upper GIB.

During the COVID-19 pandemic, COVID-19-positive patients with gastrointestinal bleeding had less often endoscopic evaluation because of a high amount of anxiety among healthcare professionals due to the high risk of aerosol transmission (especially in upper digestive endoscopy and in the pre-vaccination era), high mortality, and lack of personal protective equipment early in the pandemic; moreover, early data on COVID-19 patients showed good results in patients managed conservatively [1,22,26,28,41,42]. Another important factor that needed to be considered was the high risk of desaturation and cardiac or pulmonary complications in patients with COVID-19 pneumonia and gastrointestinal bleeding, with a potential subsequent respiratory aggravation during endoscopy and a respiratory support escalation, which was very difficult during pandemic peaks [74]. Diagnostic and especially therapeutic endoscopies were very difficult to perform when personal protective equipment was used; some patients with severe COVID-19 pneumonia and GIB were already intubated, which may have further increased the difficulty in performing endoscopy [1,20]. For these reasons, most available guidelines and hospital protocols include hemodynamic instability and a lack of response in the first 24 h as the main reasons for endoscopy [3,6,16]; a balanced approach between risks (for both patient and personnel) and benefits was preferred [8,20,21]. Increasing the threshold for endoscopic intervention may be useful, but the clinician's judgement was demonstrated to be an independent predictor of intervention, rebleeding, and mortality in patients with UGIB [47]. The accurate stratification of patient risk, including artificial intelligence using machine learning tools, may aid in the decision-making process for endoscopy [76]. Lower endoscopy rates and delayed procedures were noted in several studies; a lack of endoscopy is associated with significantly higher mortality compared to both variceal and non-variceal bleeding [19]. In our meta-analysis, the odds of upper digestive endoscopy in the first 24 h after admission in GIB patients were 0.29 lower among COVID-19-positive patients than among COVID-19-negative patients; the OR for therapeutic endoscopy was 0.68 in patients with COVID-19 infection compared to those without COVID-19, which implies that less endoscopic therapy was needed. Delays in endoscopy may have impacted the overall mortality in patients who were admitted for GIB and tested positive for COVID-19 infection; however, medical interventions for both GIB and COVID-19 infection probably plays a major role. The lower OR for diagnostic upper digestive endoscopy and endoscopic therapy is more likely related to the conservative approach to GIB in COVID-19 patients.

The main strength of our systematic review and meta-analysis is represented by the inclusion of studies containing patients admitted for GIB and diagnosed during admission with COVID-19 infection. This special category of patients can be at risk of treatment problems because of the delicate balance between early hemostasis achievement and delayed anticoagulant and anti-inflammatory therapy, which can aggravate the evolution of COVID-19 infection and potentially increase overall mortality.

The main limitation of our meta-analysis is related to the small number of included studies because most studies analyzing GIB in COVID-19-positive patients did not differentiate between admissions for GIB or COVID-19 infection; some studies reported the number of patients with GIB during admission, but lacked separate data regarding mortality. There

was also heterogeneity regarding the site of GIB; some studies included all GIB, whereas others included only UGIB. There was also some heterogeneity regarding the reporting period; most studies only included patients from the first pandemic wave, whereas only one study [21] reported cases from the first 2 years of the pandemic (including the most severe delta pandemic wave). The testing methods used for COVID-19 were variable (PCR, rapid antigen testing, or other), and there was a possibility that some negative COVID-19 cases (control group) had the infection (false-negative COVID-19 tests). The risk of publication bias may be present because the statistical tests used (funnel plots and Egger's test) have low statistical power with fewer than 10 studies, even though no asymmetry was detected. Visual inspection of the funnel plot did not suggest asymmetry, but the limitation associated with the small number of studies; therefore, the pooled estimate should be interpreted with caution. Future good quality studies, including a significant number of patients, a higher amount of variceal bleeding, and also other pandemic waves such as the alpha variant, delta variant, or omicron variant of the COVID-19 infection, may add significant accuracy to the outcomes assessment; this may be particularly valuable for the alpha and delta variants (since only one included study contained the delta variant of COVID-19) and also for the omicron variant (which is associate with a lower mortality risk but may have a significant prevalence in the future). The impact of vaccination may also represent an important issue for future research in the field of GIB and COVID-19 association, because only in one study were the vaccines available during the analyzed period.

5. Conclusions

Patients admitted for GIB and diagnosed with COVID-19 infection at admission have a higher overall mortality rate than patients without COVID-19 infection (pooled OR = 3.80), with a much lower probability of endoscopy in the first 24 h after admission and for further therapeutic endoscopy. A trend toward a lower rebleeding rate in patients with COVID-19 was noted (pooled rebleeding rate 9.4%, estimated average OR 0.60).

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/gastroent16030020/s1, Table S1: PRISMA 2020 for Abstract and Article checklist. Table S2: Included pandemic waves, type of tests used for COVID-19 infection, and bleeding-related deaths/overall deaths for in-cluded studies.

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