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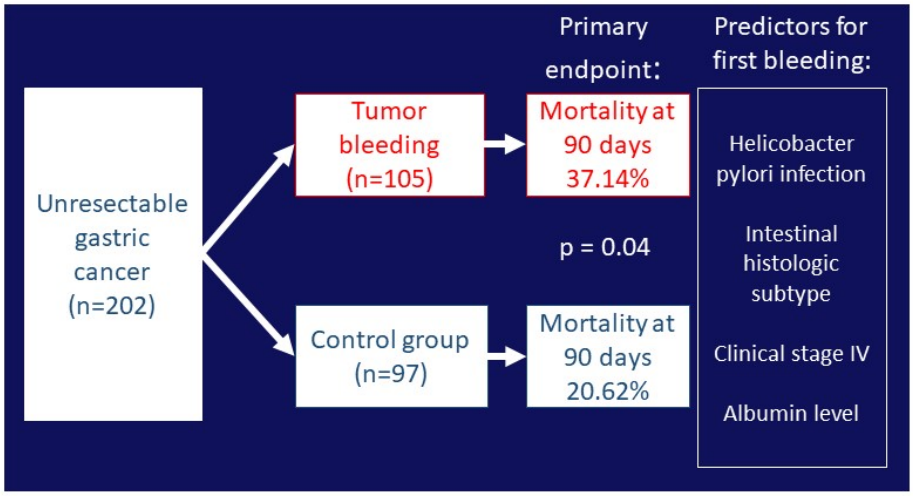

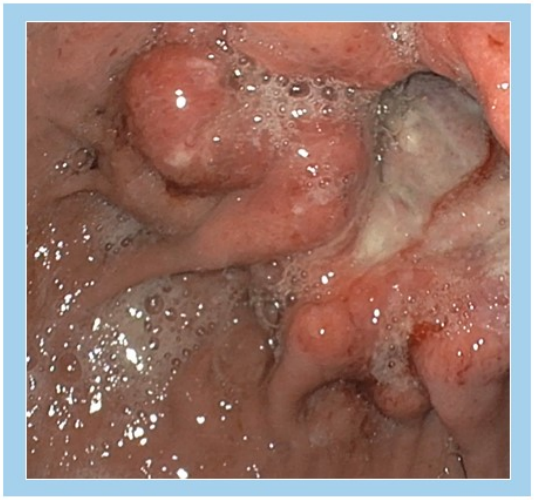

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Mortality in patients with unresectable gastric cancer complicated with tumor bleeding

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Abbreviations:

GC, gastric cancer; UGIB, upper gastrointestinal bleeding; GI, gastrointestinal bleeding; Hb, hemoglobin; uGC, unresectable gastric cancer; LA, locally advanced.

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Patient consent statement: Given that this was a retrospective study and data were collected form the consent was not needed hence not obtained.

Authors contribution:

AFE study concept and design, acquisition of data, drafting of the manuscript; BGL analysis and interpretation of data, statistical analysis; HGA, JGML, MERS and JOAL critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript.

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Abstract

Background: Gastric cancer (GC) is a gastrointestinal (GI) neoplasia which often complicates with GI bleeding. It is uncertain if bleeding worsens mortality in this group of patients.

Aims: To compare 30- and 90-day mortality in patients with unresectable GC (uGC) and tumor bleeding against patients with the same neoplasia without bleeding.

Methods: Retrospective analysis of patients with uGC with and without tumor bleeding was conducted. Survival analysis for 30- and 90-days mortality was conducted using Cox regression. Logistic regression was used to identify risk factors associated with mortality and first bleeding episodes.

Results: 202 patients were included in our analysis (105 cases). Mortality at 90 days was 37.14% for cases and 20.62% for controls (p=0.04). There was a significant difference in hazard ratio (HR) at 90 days for cases compared to controls (HR 1.95, 95%CI 1.14-3.34, p=0.02). Cases without palliative chemotherapy had the highest 90-days mortality (HR 5.43, 95%CI 2.12-13.87, p<0.01), compared to controls treated with chemotherapy. Predictors for first tumor bleeding were clinical stage IV (OR 2.93, 95%CI 1.04-8.26, p=0.04), Helicobacter pylori infection (OR 2.80, 95%CI 1.35-5.80, p<0.01) and histologic intestinal-subtype (OR2.14, 95%CI 1.07-4.30, p=0.03).

Conclusions: Tumor bleeding increases 90-days mortality in patients with uGC. Prevention of first bleeding episode might improve outcomes in these patients and recognition of high-risk patients might help decision-making.

Keywords: Gastric cancer. Tumor bleeding. Endoscopy. Mortality. Unresectable

Introduction

Gastric cancer (GC) is the fourth most common neoplasia worldwide [1]. It accounts for 5% of all upper gastrointestinal bleedings (UGIB) and almost 60% of all bleedings from upper gastrointestinal (GI) neoplasms [2]. Most GC complicated with bleeding are unresectable tumors [2-4]. UGIB secondary to GC has been treated with several endoscopic therapies

with high technical success [4], although early recurrence can appear half of the cases [5-7]. Retrospective studies have associated GC bleeding with a lower survival rate compared to patients without bleeding [4,6,8]. However, it is uncertain if bleeding itself worsens prognosis since most bleeding episodes are stable and unsuitable for endoscopic therapy [9]. Therefore, we aim to compare mortality in patients with bleeding secondary to unresectable GC (uGC) against patients who have never bled.

Methods

This was a retrospective study conducted in a Tertiary care level (Instituto Nacional de Cancerología in Mexico City). Clinical files from patients with GC who attended our Gastrointestinal Endoscopy Department from January 2018 to December 2021, were revised. The inclusion criteria were patients aged 18 years or above with a confirmed diagnosis of uGC. Patients with another histological diagnosis, gastric surgical resection, survival prognosis lower than 90 days due to other causes, or bleeding from benign etiologies were excluded.

Patients with uGC who have never bled were allocated to the control group. The case group included patients with uGC who experienced bleeding during follow-up at 30- and 90-days after their diagnosis. Follow-up started at index endoscopy (Day 0). Time from the index endoscopy to tumor bleeding, rebleeding and death was recorded. All endoscopic and histological diagnoses were performed at the referral center by advanced GI endoscopists and pathologists, respectively. EVIS EXERA III (GIF-HQ190) gastroscopes (Olympus, Tokyo, Japan) were used for endoscopic procedures. Given that this was a retrospective study, consent was not required. This study was authorized by the Local Ethic Committee of the Instituto Nacional de Cancerología in Mexico City [reference number 0406/2022].

Definitions

Tumor bleeding had two definitions: 1) a hemoglobin (Hb) drop greater than 2 g/dl within 24 hours in a patient with uGC alongside clinical signs of UGIB; or 2) an initial Hb value lower

than 10 g/dl in patients without a previous Hb result and clinical signs of UGIB. Endoscopic management was decided by the endoscopy team on a case-by-case basis. Rebleeding was defined as meeting again the first definition of UGIB and/or a decrease in Hb greater than 3 g/dl from baseline during the next 90 days after index endoscopy. Borrmann classification was used to describe endoscopic tumor morphology: polypoid (type I), ulcerated (type II), infiltrative-ulcerated tumors (type III) and diffuse infiltrative (type IV) [10]. Proximal located tumors were defined as neoplasms arising from the cardias to the incisura (gastric body), while distal located tumors were defined as neoplasms arising from the incisura to the pylorus (antrum). Extensive tumors compromised both gastric body and antrum. Histologic subtype was classified according to Lauren Classification System for Gastric Cancer into intestinal, diffuse, or mixed subtypes [11]. Clinical stage was defined as locally advanced (LA) if there was evidence of lymph node involvement and/or major vascular invasion and as metastatic (IV) if there was evidence of metastases. Differentiation grade was classified as well-differentiated (G1), moderately-differentiated (G2), poorly-differentiated (G3) and undifferentiated (G4).

Outcomes

The primary outcome was to compare mortality rate at 90-days after bleeding in patients with uGC compared to patients with the same neoplasia who have never bled. Secondary outcomes were to compare mortality rate at 30-days between both groups and to identify predictors for first tumor bleeding.

Statistical analysis

Descriptive statistics were used to describe baseline characteristics. Categorical variables were described in frequencies and percentages, while central tendency measures were used for quantitative variables. Chi-squared test was used to compare categorical variables. Student's t-test was used to compare quantitative variables.

Survival analysis using Cox regression was conducted for mortality in both groups at 30 and 90 days. Logistic regression analysis was conducted to identify predictors for 30- and 90-

days mortality and a first bleeding episode. Significant p-value was set as <0.05. Statistical analyses were conducted in IBM SPSS Statistics version 22 (IBM Corp., Armonk, New York, USA).

Results

A total of 735 electronic files from patients diagnosed with gastric tumors were identified; 202 patients met the inclusion criteria. 105 patients met our "bleeding" definitions, while the rest (97) did not (Figure 1). Complete baseline characteristics of all patients are shown in Table 1.

The mean age was 56 years with most patients (53.46%) being males. Most tumors were located proximally (68.81%), involved both gastric curvatures (48.02%) and were morphologically described as Borrmann III (48.02%). Diffuse GC was the most common histologic subtype (63.86%). 59 patients (29.21%) died during the 90-days follow-up, corresponding to 39 patients from the case group (37.14%) and 20 patients (20.62%) from the control group (p=0.04). Median survival time was 202 and 145 days for patients in the control and case group, respectively (p<0.01).

Patients with tumor bleeding

Melena was the most prevalent symptom in patients with tumor bleeding (83.81%). Only 20% of patients had active bleeding on endoscopy and 10.48% received endoscopic therapy, achieving immediate hemostasia in 9 out of 11 cases. Rebleeding at 30- and 90-days was present in 19.05% and 23.81% of patients, respectively.

Mortality at 30 and 90 days

After adjustment of 90-days mortality to different variables, we found that highest HR were for cases with intestinal-subtype (HR 2.30, 95%CI 1.20-4.39, p=0.01), extensive tumors (HR 3.33, 95%CI 1.40-7.94, p<0.01) and/or who did not receive palliative chemotherapy (HR 5.43, 95%CI 2.12-13.87, p<0.01), compared to controls with intestinal-subtype, non-

extensive tumors and who received chemotherapy, respectively. Interestingly, we did not find a difference between cases and controls with albumin level above 3.25 g/dl (HR 1.94, 95%CI 0.97-3.89, p=0.06), while both groups of patients with albumin level below 3.25 g/dl had a higher mortality hazard compared to controls with high albumin.

Table 2 shows the results of the univariate and multivariate models for 30- and 90-days mortality in all patients. Malignant ascites (OR 3.16, 95%CI 1.21-8.29, p=0.02) and hypotension (OR 9.13, 95%CI 2.03-41.13, p<0.01) were statistically significant for mortality at 30 days, while bleeding was not (OR 1.85, 95%CI 0.75–4.60, p=0.18). Chemotherapy was a protective factor for mortality at 30 days (OR 0.29, 95%CI 0.11-0.75, p=0.01).

For 90-days mortality, the main predictors were bleeding (OR 2.51, 95%CI 1.14-5.51, p=0.02) and having extensive tumor (OR 2.89, 95%CI 1.17–7.15, p=0.02). On the multivariate analysis, both factors remained statistically significant. Differences in mortality between groups at 30- and 90-days can be observed in Figure 2. A statistically significant difference in 90-days mortality was observed between groups with a hazard ratio (HR) 1.95 (95%CI 1.14–3.34, p=0.02) for patients with bleeding. No additional predictors were identified for mortality at 90 days in patients with tumor bleeding.

First and rebleeding episodes

In the multivariate model, *H. pylori* infection (OR 2.80, 95%CI 1.35-5.80, p<0.01), intestinal histologic subtype (OR 2.14, 95%CI 1.07-4.30, p=0.03) and a clinical stage IV (OR 2.93, 95%CI 1.04-8.26, p=0.04) were statistically significant for presenting the first episode of bleeding, while albumin levels above 3.25 g/dl (OR 0.15, 95%CI 0.07-0.33, p<0.01) was a protective factor (Table 3).

Discussion

We investigated the role of tumor bleeding in patients with uGC and found that it significantly increases mortality at 90 days since index endoscopy. Approximately 70 % of

patients with uGC develop tumor bleeding and our results are in line with previous investigations [12]. The impact of bleeding from uGC has been previously described by others, reporting a decreased survival (6.5 vs 18.5 months) for these patients [6], which is similar to our findings (145 vs 202 days). However, bleeding episodes from uGC are typically low-grade (mild bleeding, without different outcomes after endoscopic interventions) or inactive by the time of endoscopy [9,13], which makes unclear if these events increase mortality by themselves. Furthermore, the fact that we did not observe a higher mortality risk at 30 days in the case group (HR 1.80, 95%CI 0.76-4.24, p=0.18) supports that tumor bleeding is rarely life-threatening, as has been recently reported [14], and contrary to what others have described [9]. However, hemodynamic instability during the event has a role as the strongest predictor for short-term mortality (OR 6.18, 95%CI 1.44–26.54, p=0.01; data not shown as it was the only predictor for mortality in this group). The latter has been already described for both benign and malignant UGIB [12,15,16].

With regard to tumor extension, extensive tumors carry a worse 90-days prognosis, increasing mortality risk for all patients, but being the highest for the case group. We are not aware that this precise finding has been previously described, but others have reported that tumor size is an independent prognostic factor [17]. Intestinal-subtype has been associated to better outcomes than diffuse GC, especially in advanced stages [18], as we showed how our control group with intestinal-subtype GC carried the lowest mortality risk. Nevertheless, it is interesting how tumor bleeding increases mortality in this subgroup of patients, possibly related to distinct tumor biology and/or its association to *H. pylori* [19]. To our knowledge, this finding has not been reported before. Patients with tumor bleeding without chemotherapy had the highest mortality risk. However, similar HR were observed for controls without chemotherapy and even cases with chemotherapy; all the latter groups had significantly higher HR compared to controls with chemotherapy. Benefits of chemotherapy in uGC have been extensively discussed, along to its limitation in the setting of tumor bleeding [20]. Lastly, albumin is recognized as a prognostic biomarker in oncology

[21,22]; our results suggest that high albumin levels cancel the impact of tumor bleeding on 90-days mortality. Prospective studies are needed to confirm these results.

In addition, we have identified several predictors for a first episode of tumor bleeding, including intestinal-subtype, clinical stage IV and active *H. pylori* infection. Park et al have already described that metastatic disease is a risk factor for bleeding [6], but to our knowledge, this is the first time that *H. pylori* infection has been identified as a predictor for bleeding in uGC. In contrast, we did not find an association between Borrmann classification and risk of tumor bleeding [6]. Furthermore, and in line with others, we did not find any benefit from proton pump inhibitors prescription in these patients [23].

Our study has several strengths. All records were available, allowing us to assess events of bleeding from the index endoscopy until the end of follow-up. All patients had an index endoscopy performed with high-definition gastroscopes, detailed written reports and biopsy samples that allowed us to confirm the diagnosis of GC, endoscopic features of tumors and histologic subtypes. Every tumor bleeding episode was confirmed with endoscopic examination and other etiologies for bleeding were excluded.

Limitations to this study are its retrospective nature and the fact that all patients were Hispanics, so external validation is mandatory for assessing our findings in other populations.

In conclusion, our results indicate that patients with uGC and tumor bleeding have a higher 90-days mortality risk, which supports that tumor bleeding is rarely an acutely life-threatening event and more of a subacute, weakening condition. Patients with intestinal-subtype, extensive tumors and absence of chemotherapy might be subgroups of higher risk. Strategies should aim to avoid factors for first bleeding. Validation of our results in further studies might help decision-making for clinicians.

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Conflict of interest

The authors declare no conflict of interest.

References

1. Ajani JA, Lee J, Sano T, et al. Gastric adenocarcinoma. Nat Rev Dis Primers. 2017;3:17036. DOI:10.1038/nrdp.2017.36
2. Kim Y, Choi I. Endoscopic management of tumor bleeding from inoperable gastric cancer. Clin Endosc. 2015;48(2):121-127. DOI:10.5946/ce.2015.48.2.121
3. Vasas P, Wiggins T, Chaudry A, et al. Emergency presentation of the gastric cancer; prognosis and implications for service planning. World J Emerg Surg. 2012;7(1):31. Doi: 10.1186/1749-7922-7-31.
4. Kim Y, Choi I, Cho SJ, et al. Outcome of endoscopic therapy for cancer bleeding in patients with unrsectable gastric cancer. J Gastroenterol Hepatol. 2013;28(9):1489-95. DOI: 10.1111/jgh.12262.
5. Koh KH, Kim K, Kwon DH, et al. The successful endoscopic hemostasis factors in bleeding from advanced gastric cancer. Gastric Cancer. 2013;16(3):397-403. DOI:10.1007/s10120-012-0200-3
6. Park H, Ahn JY, Jung HY, et al. Can endoscopic bleeding control improve the prognosis of advanced gastric cancer patients? A retrospective case-control study. 2017;51(7):599-606. DOI: 10.1097/mcg.0000000000000717.
7. Beg S, Al-Bakir I, Bhuva M, et al. Early clinical experience of the safety and efficacy of endoclot in the management of non-variceal upper gastrointestinal bleeding. Endosc Int Open. 2015;3(6):E605-E609. DOI:10.1055/s-0034-1393087.

8. Song IJ, Kim HJ, Lee JA, et al. Clinical outcomes of endoscopic hemostasis for bleeding in patients with unresectable advanced gastric cancer. J Gastric Cancer. 2017;17(4):374-383. DOI:10.5230/jgc.2017.17.e42
9. Maluf-Filho M, Martins BC, de Lima MS, et al. Etiology, endoscopic management and mortality of upper gastrointestinal bleeding in patients with cancer. United European Gastroenterol J. 2013;1(1):60-7. Doi: https://doi.org/10.1177/2050640612474652.
10. Borchard FJ. Classification of gastric carcinoma. Hepatogastroenterology. 1990;37(2):223-232.
11. Lauren P. The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma. An attempt at a histo-clinical classification. Acta Pathol Microbiol Scand. 1965;64:31-49. Doi: 10.1111/apm.1965.64.1.31.
12. Sheibani S, Kim JJ, Chen B, et al. Natural history of acute upper gi bleeding to tumours: short-term success and long-term recurrence with or without endoscopic therapy. Aliment Pharmacol Ther. 2013;38(2):144-50. Doi: https://doi.org/10.1111/apt.12347.
13. Kim YI, Choi IJ, Lee JY, et al. Comparison of the performance of risk scoring systems for tumor bleeding in patients with inoperable gastric cancer. Endoscopy. 2020;52:359-367. Doi: https://doi.org/10.1055/a-1114-6000.
14. Karna R, Deliwala S, Ramgopal B, et al. Efficacy of topical hemostatic agents in malignancy-related GI bleeding: a systematic review and meta-analysis. Gastrointest Endosc. 2023;97(2):202-208. Doi: https://doi.org/10.1016/j.gie.2022.07.033.
15. Saltzman JR, Tabak YP, Hyett BH, et al. A simple risk score accurately predicts in-hospital mortality, length of stay, and cost in acute upper gi bleeding. Gastrointest Endosc. 2011;74(6):1215-24. Doi: https://doi.org/10.1016/j.gie.2011.06.024.
16. Stanley AJ, Laine L. Management of upper gastrointestinal bleeding. BMJ. 2019;25:364:l536. Doi: https://doi.org/10.1136/bmj.l536.
17. Wang HM, Huang CM, Zheng CH, et al. Tumor size as a prognostic factor in patients with advanced gastric cancer in the lower third of the stomach. World J Gastroenterol. 2012;18(38):5470-5475. Doi: https://doi.org/10.3748/wjg.v18.i38.5470.

18. Bamboat ZM, Tang LH, Vinuela E, et al. Stage-stratified prognosis of signet ring cell histology in patients undergoing curative resection for gastric adenocarcinoma. Ann Surg Oncol. 2014;21(5):1678-85. Doi: https://doi.org/10.1245/s10434-013-3466-8.
19. Uemura N, Okamoto S, Yamamoto S, et al. Helicobacter pylori infection and the development of gastric cancer. N Engl J Med. 2001;345(11):784-9. Doi: https://doi.org/10.1056/nejmoa001999.
20. Ajani JA, D'Amico TA, Bentrem DJ, et al. Gastric cancer, version 2.2022, nccn clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2022;20(2):167-192. Doi: https://doi.org/10.6004/jnccn.2022.0008.
21. Hu CG, Hu BE, Zhu ZM, et al. Prognostic significance of the preoperative hemoglobin to albumin ratio for the short-term survival of gastric cancer patients. World J Gastrointest Surg. 2022;14(6):580-593. Doi: https://doi.org/10.4240/wjgs.v14.i6.580.
22. Fang N, Zhang HQ, He B, et al. Clinicopathological characteristics and prognosis of gastric cancer with malignant ascites. Tumour Biol. 2014;35(4):3261-8. Doi: https://doi.org/10.1007/s13277-013-1426-3.
23. Kim YI, Kim MJ, Park SR, et al. Effect of a proton pump inhibitor on tumor bleeding prevention in unresectable gastric cancer patients: a double-blind, randomized, placebo-controlled trial. J Gastric Cancer. 2017;17(2):120-131. Doi: https://doi.org/10.5230/jgc.2017.17.e15.

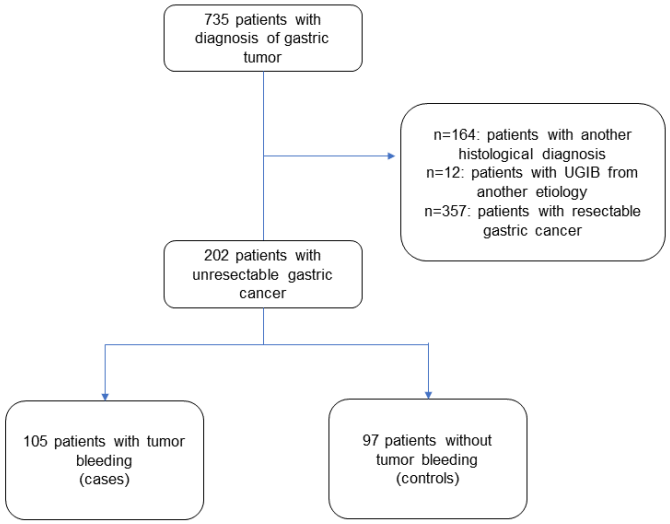

Figure 1. Flowchart of patient inclusion.

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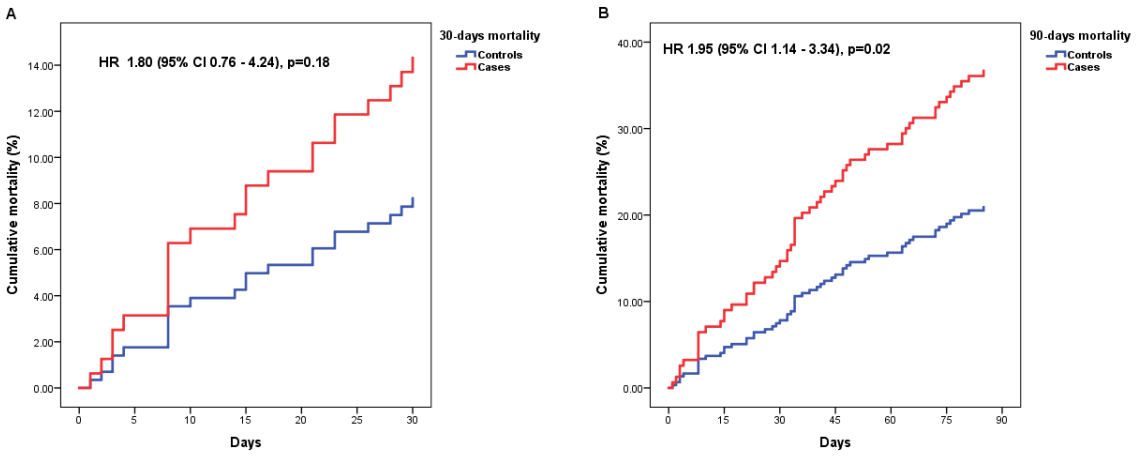

Figure 2. Mortality at 30 (A) and 90 (B) days from index endoscopy for controls and cases.

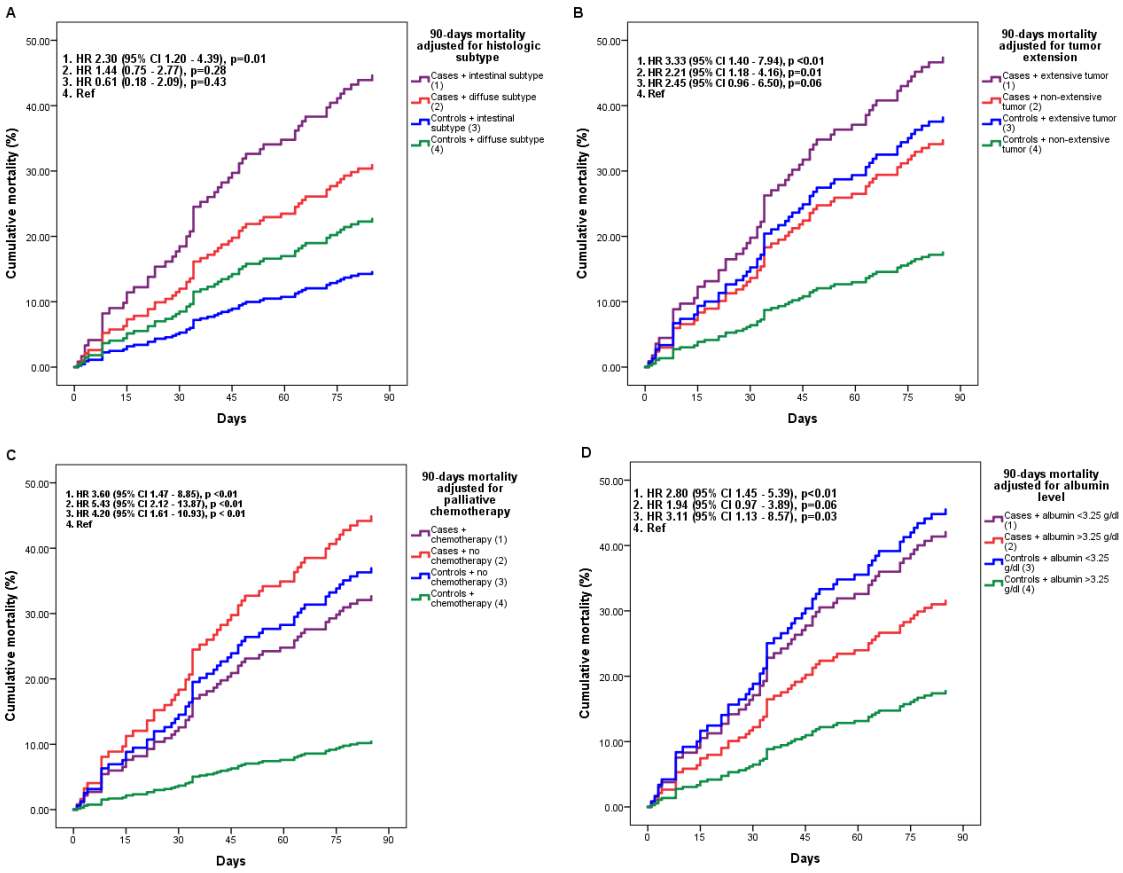

Figure 3. Mortality at 90 days adjusted for histologic subtype (A), tumor extension (B), palliative chemotherapy (C) and albumin level (D).