Impact of the coronavirus disease 2019 pandemic on the management of acute peptic ulcer perforation: to be reconsidered(?)

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SUMMARY

OBJECTIVE: Peptic ulcer perforation presents the most serious complication of ulcer disease with mortality that varies significantly depending on the age and conditions. The coronavirus disease 2019 pandemic was effective worldwide in 2020 and continues to date. The aim of this study was to investigate the initial clinical parameters and short-term outcomes of patients with acute peptic ulcer perforation before and during the coronavirus disease 2019 pandemic.

METHODS: A retrospective cohort study was conducted in the Department of Surgery, University Hospital Ostrava, Czech Republic. The patients undergoing surgical modality of a simple suture of peptic ulcer perforation with/without omentoplasty in the post-coronavirus disease 2019 (January 1, 2020 to December 31, 2021) and the pre-coronavirus disease 2019 (January 1, 2018 to December 31, 2019) had been incorporated in this study. RESULTS: This study included a total of 46 cases (26 in the pre-coronavirus disease 2019, 20 in the post-coronavirus disease 2019). The age, body mass index, Boey score, duration of symptoms, surgery time, and length of hospital stay were comparable in both study subgroups. During the coronavirus disease 2019 pandemic, patients were admitted with a statistically significantly lower degree of perioperative risk according to the American Society of Anesthesiologists classification (p=0.013). Notably, 30-day postoperative morbidity was significantly higher in pre-coronavirus disease 2019 (73.1 vs. 55.0%, p=0.038). The mortality rate in the laparoscopic group was 13.6%, in the laparotomy group 41.4%, and the mortality rate was higher in pre-coronavirus disease 2019 than in post-coronavirus disease 2019 (34.6 vs. 20.0%, p=0.166).

CONCLUSION: In fact, the coronavirus disease 2019 pandemic had not significantly influenced therapeutic management and short-term outcomes of patients undergoing acute surgical repair of peptic ulcer perforation.

KEYWORDS: Peptic ulcer perforation. COVID-19. Pathology. Mortality. Morbidity.

INTRODUCTION

Peptic ulcer (PU) disease is the most common disease of the upper gastrointestinal tract with a worldwide incidence of about 90 cases per 100,000 inhabitants per year. The most serious and life-threatening complication of PU disease is perforation, the worldwide average incidence of which is approximately 9 cases per 100,000 inhabitants¹. The mortality of PU perforation is generally around 10–40%^{2,3} but varies significantly depending on the patient's age and condition prior to and at the moment of admission to the hospital. For the patient with PU perforation, some specific classification systems can be used to

determine the degree of risk of a patient with PU perforation. Currently, the simple and accurate Boey score is used mainly for this purpose⁴. The standard treatment option for patients with PU perforation is a surgical suture of perforation, which can be performed by laparotomy or using minimally invasive surgical techniques.

The coronavirus disease 2019 (COVID-19) pandemic affected the whole world in 2020 and continues to date. In total, more than half a billion people have been proven to be infected. Although the number of reported deaths from COVID-19 reached 5.94 million worldwide at the end of

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2021, it is estimated that up to 18.2 million people worldwide have died from the disease to this date (95%CI 17.1–19, 6)⁵. The Czech Republic, similar to Brazil, had one of the highest incidences of disease and subsequent mortality per million inhabitants in the world⁶.

In addition to wearing masks, the basic mechanism of the fight against COVID-19 was the isolation of the population. Due to the isolation of the population and the overload of the health system, patients with PU disease temporarily lost the possibility of these regular checks and examinations that could have resulted in a deterioration of their health status, stress, and an augmentation in the risk of subsequent complications, including acute PU perforation. Recently, some studies have suggested a change in the spectrum of patients and treatment modality for acute conditions during the pandemic period. These studies reported an attenuated number of patients with acute problems, but an increase in their more severe conditions⁷⁻⁹.

The aim of this study was to investigate the initial clinical parameters and the short-term outcomes of patients undergoing acute surgical repair of PU perforation pre- and post-COVID-19. We ask ourselves whether the COVID-19 pandemic affected the availability of acute care for patients with PU perforation and, therefore, worsened their condition before admission and subsequently increased the risk of postoperative complications and mortality.

METHODS

A retrospective cohort study with a total of 46 cases had been conducted in the Department of Surgery, University Hospital Ostrava, Ostrava, Czech Republic. To this end, the cases undergoing surgical repair, the simple suture of PU perforation, with or without omentoplasty in the post-COVID-19 (January 1, 2020 to December 31, 2021) and the pre-COVID-19 (January 1, 2018 to December 31, 2019) had been incorporated in this study. All the cases had undergone simple acute surgical closure of PU perforation with or without omentoplasty by conventional or laparoscopic approach. In addition, the cases with different or other associated procedures and with incomplete data in the hospital document database had been excluded from the present study design.

Demographic and clinical data from all the studied cases, such as the age, sex, body mass index (BMI), American Society of Anesthesiologists (ASA) classification, duration of symptoms of PU perforation, surgical modality, surgery time, length of hospital stay, and 30-day postoperative morbidity were extracted from hospital medical records. The preoperative clinical condition of all the cases had been assessed according to the Boey

score (Table 1). The duration of perforation was determined as the time interval between the onset of severe acute abdominal pain and arrival time at the hospital. Systolic blood pressure <100 mmHg was considered a preoperative shock and the health conditions of systemic heart, lung, liver, or kidney disease, cancer, and diabetes were considered concomitant severe medical illnesses¹⁰. The postoperative complications were classified according to the Clavien-Dindo classification¹¹.

The obtained data were analyzed using descriptive statistics (mean, standard deviation, median, range, relative frequency). The Student's t-test or the Mann-Whitney U test was used for quantitative variables while the χ^2 test was used for the categorical variables. A level of significance of α =0.05 and p<0.05 were considered statistically significant.

RESULTS

The study included a total of 46 cases after the surgical suturation of the PU perforation. In the pre-COVID-19 (which was considered the reference period), 26 cases had been included while 20 were in the post-COVID-19. The basic demographic and clinical characteristics of all the studied patients are presented in Table 2. No statistically significant differences between the pre- and post-COVID-19 in age (p=0.164), BMI (p=0.288), or surgical modality (p=0.249) were recognized.

Regarding the Boey score and ASA classification, patients in post-COVID-19 had better general health status at the moment of hospital admission. Herein, 50.0% of the cases in post-COVID-19 had a Boey score of 0 and no one had a Boey score of 3. In contrast, 15.4% of the cases in the pre-COVID-19 had a Boey score of 3, and solely 26.9% had a Boey score of 0. Notably, the differences in Boey scores between the study subgroups were not statistically significant (p=0.207). Similarly, 35.0% of the cases of post-COVID-19 were preoperatively classified as ASA I–II and only 15.0% as ASA IV–V. In contrast, only 19.2% of patients in pre-COVID-19 were classified as ASA I-II and 50.0% as ASA IV-V. The differences in ASA classification between the study subgroups were statistically significant (p=0.013). The average duration of symptoms of perforation was 24.1±21.8 h in 43.5% of the cases with perforation lasting longer than 24 h and the differences

Table 1. The Boey score.

Boey score	Findings		
1 point	Duration of perforation >24 h		
1 point	Preoperative shock		
1 point	Concomitant severe medical illness		

in the duration of perforation between study subgroups were not significant (p=0.365, p=0.188).

The intra- and postoperative outcomes are presented in Table 3. The average operation time was 53.0±17.7 min, and the difference between the subgroups was not statistically significant (p=0.291). The mean postoperative hospital stay was 13.0±8.6 days (13.6±8.9 days, post-COVID-19 and 12.6±8.6 days, pre-COVID-19 with a range of 3–35 days), which did not reveal any significance (p=0.720). In addition, the 30-day

postoperative morbidity rate was 65.2%, whereas 55.0% in post-COVID-19 and 73.1% in pre-COVID-19 had possessed postoperative complications with a statistical significance in the postoperative morbidity rate (p=0.038). The severity of postoperative complications between the subgroups was not significant considering the Clavien-Dindo classification (p<0.0112). Besides, 30-day postoperative mortality was 28.3%, which was higher in patients in pre-COVID-19 compared to post-COVID-19, without significance (34.6 vs. 20.0%, p=0.166).

Table 2. The demographics and clinical data of the studied cases.

	Post-COVID-19 n=20	Pre-COVID-19 n=26	р	Total n=46
Age, years, mean±SD	58.8±17.7	65.8±14.7	0.164	62.7±16.3
Gender, n (%)			1.000	
Female	7 (35.0%)	10 (38.5%)		17 (37.0%)
Male	13 (65.0%)	16 (61.5%)		29 (63.0%)
BMI (kg/m²), mean±SD	22.6±4.4	24.2±5.2	0.288	23.5±4.9
ASA, n (%)			0.013	
1-11	7 (35.0%)	5 (19.2%)		12 (26.1%)
III	10 (50.0%)	8 (30.8%)		18 (34.8%)
IV-V	3 (15.0%)	13 (50.0%)		16 (39.1%)
Boey score, n (%)	0.207			
0	10 (50.0%)	7 (26.9%)		17 (37.0%)
1	4 (20.0%)	6 (23.1%)		10 (21.7%)
2	6 (30.0%)	9 (34.6%)		15 (32.6%)
3	0 (0.0%)	4 (15.4%)		4 (8.7%)
Duration of symptoms, h, mean±SD	20.7±23.1	26.7±20.9	0.365	24.1±21.8
Duration of perforation >24 h, n (%)	6 (30.0%)	14 (53.8%)	0.188	20 (43.5)
Surgery approach, n (%)			0.249	
Laparoscopy	12 (60.0%)	10 (38.5%)		22 (47.8%)
Laparotomy	8 (40.0%)	16 (61.5%)		24 (52.2%)

Table 3. The intraoperative and postoperative outcomes of study patients.

	Post-COVID-19 n=20	Pre-COVID-19 n=26	р	Total n=46
Surgery time (min, mean±SD)	49.6±17.1	55.4±18.0	0.291	53.0±17.7
Length of hospital stay (day, mean±SD)	13.6±8.9	12.6±8.6	0.720	13.0±8.6
30-Day postoperative morbidity, n (%)	11 (55.0%)	19 (73.1%)	0.038	30 (65.2%)
Clavien-Dindo classification, n (%)			0.112	
Grade 0	9 (45.0%)	7 (26.9%)		16 (39.1%)
Grades I-II	4 (20.0%)	5 (19.2%)		9 (19.6%)
Grades III-IV	3 (15.0%)	5 (19.2%)		8 (17.4%)
Grade V (postoperative mortality)	4 (20.0%)	9 (34.6%)	0.166	13 (28.3%)

DISCUSSION

Patients with COVID-19 overwhelmed hospitals, which had to attenuate care for the remaining patients. This might have worsened the care of chronic patients and augmented the risk of hidden problems turning into acute and life-threatening conditions. A good example of the effect of delayed care on chronic patients is reported by Mun et al.'s¹² study in 2021. The authors expressed a set of 1,453 cases with chronic pain due to the postponement or cancellation of all regular checkups and the restriction of access to prescription opioids during the COVID-19 period, where approximately 25–30% of individuals reported exacerbation of their chronic pain. Similar conclusions were also described by Pagé et al.¹³, Chatkoff et al.¹⁴, and Lang-Illievich et al.¹⁵.

The deterioration in care for patients without COVID-19 can be found in all medicines. Some authors ^{16,17} described an increase in the numerical value of seizures and a worsening of sleep quality in cases with epilepsy during the COVID-19 period. Rabbone et al. ¹⁸ reported that the COVID-19 pandemic could have altered diabetes presentation, whereas Brown et al. ¹⁹ showed disrupted medical care, exercise, and social activities that led to worsening of motor and nonmotor symptoms in about half of the cases.

The neglect of care for patients without COVID-19 was also reflected in surgery. Serban et al.20 investigated the effects of the COVID-19 pandemic on the clinical presentation and therapeutic management of acute surgical abdomen. They found that the number of patients with therapeutically neglected or undiagnosed colorectal cancer who developed urgent complications such as tumor obstruction or perforation increased during the pandemic period^{21,22}. The change in the frequency of the most frequent acute surgical diagnoses was investigated by Cano-Valderrama et al.²³, who reported that a significant reduction was observed in the number of acute surgery procedures performed and the delay in the arrival of patients in the hospital during the pandemics²⁴⁻²⁵. Higher morbidity was observed in patients undergoing acute surgery during the pandemic period, although mortality did not change. Herein, our study noted a slight decrease in the incidence of acute PU perforation during the pandemic period but did not observe a delay in the arrival of patients to the hospital or a worsening of their clinical condition at the time of admission.

To the best of our knowledge, no study has reported the effects of health restrictions during the COVID-19 pandemic on the treatment of acute PU perforation in the English-language literature. Preliminary outcomes of this study exhibited that during the COVID-19 pandemic there was no expected increase in PUP cases; in contrast, a slight decrease

might be due to the patients' fear of visiting the hospital during the pandemic. Herein, an important question is whether the change in the demographic curve of the population is behind the decline. As is known, mainly older and already ill people died from COVID-19; hence, the population most at risk of complications from ulcer disease was significantly attenuated by the pandemic. Therefore, fewer patients at risk for PU disease complications may have led to a lower incidence of PU perforation in the era of COVID-19.

The alterations in the demographic curve can also explain some of the outcomes of the present study. In post-COVID-19, younger patients and patients with a lower average BMI (than those pre-COVID-19) came to the hospital. However, this change was not statistically significant, and, therefore, we cannot take it as the result of an alteration in the distribution of the studied population. In contrast, post-COVID-19, patients came to the hospital with a statistically significantly lower degree of risk according to the ASA classification, indicating the selection of a relatively healthier population compared with pre-COVID-19. The higher number of cases with a low degree of risk according to the Boey score in post-COVID-19 can be explained similarly.

The better clinical condition of the patients post-COVID-19 was also reflected in their postoperative outcomes. We recorded a statistically significantly lower overall patient 30-day postoperative morbidity in post-COVID-19, and the cases in post-COVID-19 had significantly more often an uncomplicated postoperative course or a lower grade complication according to the Clavien-Dindo classification. Contrary to the expectation that the mortality of patients with PU perforation would increase during the pandemic period, we recorded a substantial decrease. Mortality in patients in post-COVID-19 was lower, which might be explained by the better clinical condition and the younger age of patients at admission to the hospital.

Limitations

The main limitations of the study are the size of the data set, in which a trend is clearly visible but without statistical significance, and the retrospective study design.

CONCLUSION

The therapeutic management of patients with PU perforation has not been significantly influenced by the COVID-19 pandemic. In contrast, we have recorded a better clinical condition of patients before admission to the hospital and lower postoperative morbidity/mortality after the surgical repair of

PU perforation. It might be explained by the alteration in the demographic distribution of the study population as a result of the COVID-19 pandemic. Finally, we postulate that it is critical for physicians and health providers to stay informed of the growing spectrum and clinical presentation of PU issues in this pandemic to ensure appropriate clinical care and the relevant treatment modalities to minimize both disease-induced injury and disease transmission.

AUTHORS' CONTRIBUTIONS

LT: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Validation, Visualization,

Writing – original draft. **IS:** Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – review & editing. **PI:** Investigation, Methodology, Project administration, Resources, Validation, Visualization. **MM:** Investigation, Methodology, Project administration, Resources, Validation, Visualization. **DT:** Investigation, Methodology, Project administration, Resources, Validation, Visualization. **AP:** Conceptualization, Investigation, Methodology, Project administration, Resources, Validation, Visualization. **LM:** Investigation, Methodology, Project administration, Resources, Validation, Visualization. **DS:** Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – review & editing.

REFERENCES

- Wakayama T, Ishizaki Y, Mitsusada M, Takahashi S, Wada T, Fukushima Y, et al. Risk factors influencing the short-term results of gastroduodenal perforation. Surg Today. 1994;24(8):681-7. https://doi.org/10.1007/BF01636772
- Christensen S, Riis A, Nørgaard M, Sørensen HT, Thomsen RW. Short-term mortality after perforated or bleeding peptic ulcer among elderly patients: a population-based cohort study. BMC Geriatr. 2007;7:8. https://doi.org/10.1186/1471-2318-7-8
- Noguiera C, Silva AS, Santos JN, Silva AG, Ferreira J, Matos E, et al. Perforated peptic ulcer: main factors of morbidity and mortality. World J Surg. 2003;27(7):782-7. https://doi.org/10.1007/s00268-003-6645-0
- Boey J, Choi SK, Alagaratnam TT, Poon A. A prospective validation of predictive factors. Ann Surg. 1987;205(1):22-6. https://doi. org/10.1097/00000658-198701000-00005
- COVID-19 Excess Mortality Collaborators. Estimating excess mortality due to the COVID-19 pandemic: a systematic analysis of COVID-19-related mortality, 2020–21. Lancet. 2022;399(10334):1513-36. https://doi.org/10.1016/S0140-6736(21)02796-3
- Johns Hopkins Coronavirus Resource Center. Johns hopkins coronavirus resource center. Baltimore (MD): Johns Hopkins Coronavirus Resource Center; 2020. Available from: https:// coronavirus.jhu.edu/
- Zheng ZX, Bi JT, Liu YQ, Cai X. The impact of COVID-19 pandemic on the treatment of acute appendicitis in China. Int J Colorectal Dis. 2021;37(1):215-9. https://doi.org/10.1007/s00384-021-04031-4
- Pogorelić Z, Anand S, Žuvela T, Singh A, Križanac Z, Krishnan N. Incidence of complicated appendicitis during the COVID-19 pandemic versus the pre-pandemic period: a systematic review and meta-analysis of 2,782 pediatric appendectomies. Diagnostics (Basel). 2022;12(1):127. https://doi.org/10.3390/ diagnostics12010127
- Calvão J, Amador AF, Costa CM, Araújo PM, Pinho T, Freitas J, et al. The impact of the COVID-19 pandemic on acute coronary syndrome admissions to a tertiary care hospital in Portugal. Rev Port Cardiol. 2022;41(2):147-52. https://doi.org/10.1016/j. repc.2021.01.007

- Boey J, Choi SK, Alagaratnam TT, Poon A. A prospective validation of predictive factors. Ann Surg. 1987;205(1):22-32. https://doi. org/10.1097/00000658-198701000-00005
- Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, et al. The Clavien-Dindo classification of surgical complications. Ann Surg. 2009;250(2):187-96. https://doi. org/10.1097/SLA.0b013e3181b13ca2
- 12. Mun CJ, Campbell CM, McGill LS, Aaron RV. The early impact of COVID-19 on chronic pain: a cross-sectional investigation of a large online sample of individuals with chronic pain in the United States, April to May, 2020. Pain Med. 2021;22(2):470-80. https://doi.org/10.1093/pm/pnaa446
- 13. Pagé MG, Lacasse A, Dassieu L, Hudspith M, Moor G, Sutton K, et al. A cross-sectional study of pain status and psychological distress among individuals living with chronic pain: the Chronic Pain & COVID-19 Pan-Canadian Study. Health Promot Chronic Dis Prev Can. 2021;41(5):141-52. https://doi.org/10.24095/hpcdp.41.5.01
- 14. Chatkoff DK, Leonard MT, Najdi RR, Cruga B, Forsythe A, Bourgeau C, et al. A brief survey of the COVID-19 pandemic's impact on the chronic pain experience. Pain Manag Nurs. 2022;23(1):3-8. https://doi.org/10.1016/j.pmn.2021.10.003
- Lang-Illievich K, Rumpold-Seitlinger G, Szilagyi IS, Dorn C, Sailer M, Schittek GA, et al. Biological, psychological, and social factors associated with worsening of chronic pain during the first wave of the COVID-19 pandemic: a cross-sectional survey. Br J Anaesth. 2021;127(1):e37-9. https://doi.org/10.1016/j. bja.2021.04.010
- 16. Assenza G, Lanzone J, Brigo F, Coppola A, Di Gennaro G, Di Lazzaro V, et al. Epilepsy care in the time of COVID-19 pandemic in Italy: risk factors for seizure worsening. Front Neurol. 2020;11:737. https://doi.org/10.3389/fneur.2020.00737
- 17. Rosengard JL, Donato J, Ferastraoaru V, Zhao D, Molinero I, Boro A, et al. Seizure control, stress, and access to care during the COVID-19 pandemic in New York City: the patient perspective. Epilepsia. 2020;62(1):41-50. https://doi.org/10.1111/epi.16779
- Rabbone I, Schiaffini R, Cherubini V, Maffeis C, Scaramuzza A, Bertelli E, Diabetes Study Group of the Italian Society for Pediatric Endocrinology and Diabetes. Has COVID-19 delayed the diagnosis and

- worsened the presentation of type 1 diabetes in children? Diabetes Care. 2020;43(11):2870-2. https://doi.org/10.2337/dc20-1321
- Brown EG, Chahine LM, Goldman SM, Korell M, Mann E, Kinel DR, et al. The effect of the COVID-19 pandemic on people with parkinson's disease. J Parkinsons Dis. 2020;10(4):1365-77. https://doi.org/10.3233/JPD-202249
- Serban D, Socea B, Badiu C, Tudor C, Balasescu S, Dumitrescu D, et al. Acute surgical abdomen during the COVID-19 pandemic: clinical and therapeutic challenges. Exp Ther Med. 2021;21(5):519. https://doi.org/10.3892/etm.2021.9950
- Máca J, Peteja M, Reimer P, Jor O, Šeděnková V, Panáčková L, et al. Surgical injury: comparing open surgery and laparoscopy by markers of tissue damage. Ther Clin Risk Manag. 2018;14:999-1006. https://doi.org/10.2147/TCRM.S153359
- **22.** Ihnát P, Tulinský L, Jonszta T, Koscielnik P, Ihnát Rudinská L, Penka I. Parastomal and incisional hernia following laparoscopic/

- open abdominoperineal resection: is there a real difference? Surg Endosc. 2019;33(6):1789-94. https://doi.org/10.1007/s00464-018-6453-0
- 23. Cano-Valderrama O, Morales X, Ferrigni CJ, Martín-Antona E, Turrado V, García A, et al. Acute care surgery during the COVID-19 pandemic in Spain: changes in volume, causes and complications. A multicentre retrospective cohort study. Int J Surg. 2020;80:157-61. https://doi.org/10.1016/j.ijsu.2020.07.002
- 24. Aydin I, Kesicioglu T, Vural S, Gulmez M, Sengul D, Sengul I. Analysis of patients with emergency surgery in a pandemic hospital. Ann Ital Chir. 2022;93:254-8. PMID:35476755
- 25. Kesicioglu T, Sengul I, Aydın I, Vural S, Sengul D. Management of appendicitis in coronavirus disease 19, severe acute respiratory syndrome coronavirus 2, pandemic era: decreasing incidence with increasing complicated cases? Rev Assoc Med Bras (1992). 2022;68:685-90. Available from: https://www.scielo.br/j/ramb/a/hcGDgYKtNyvL675fK86pDvz/abstract/?lang=en

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