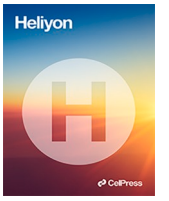
Heliyon 9 (2023) e22043

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Effects of novel Coronavirus (COVID-19) on presentation, management, and outcomes of acute cholecystitis at an academic tertiary care center cholecystitis management during COVID-19

Nicholas V. Peters [a], Rick O'Connor [a], Bishwajit Bhattacharya [a,b], John W. Kunstman [a,b,*]

[a] Yale School of Medicine, Department of Surgery, PO Box 208062, New Haven, CT 06520, USA
[b] VA Connecticut Medical Center, Department of Surgery, Bldg 1, 4th Floor, 950 Campbell Avenue, West Haven, CT 06516, USA

ARTICLE INFO

Keywords:
COVID
Acute care surgery
Perioperative management

ABSTRACT

Background: The COVID-19 pandemic necessitated adjustments to nearly all aspects of healthcare, including surgical care. The effects of these adjustments have not been well studied on acute surgical problems conventionally managed non-electively in large, tertiary care centers.
Methods: A retrospective analysis of admitted patients with acute cholecystitis at a US academic tertiary care center was performed. We compared the presentation, management, and 30-day outcomes of patients admitted during a 2-month time period during early COVID, to a pre-COVID control group of admitted cholecystitis patients over a 2-month span.
Results: The study cohort captured 24 patients, while the control cohort encompassed 53 patients. A non-significant trend toward non-operative management in the COVID cohort is reported. There was no delay in time-to-surgery or complication rate. No surgically managed patient developed COVID within 30 days of operation.
Conclusions: Operative management of acute cholecystitis during the COVID-19 pandemic, with pre-operative testing and personal protective equipment guidelines, remained safe and effective.

1. Introduction

In December 2019 a new, unusual respiratory illness was reported in Wuhan City, Hubei Province, China which was retrospectively identified as the novel COVID-19 disease [1]. The combination of COVID-19's robust transmission capability and the inter-connectedness of modern society led to rapid spread and an unprecedented global pandemic [2]. Health systems and individual hospitals worldwide faced extraordinary challenges including shortages in diagnostic testing, inadequate ICU and ventilator capacity, and widespread scarcity of both healthcare resources and providers [3–5].

To combat the rapid spread of COVID-19, countless policies have been enacted on the international, national, state, and local levels. Many of these policies have been based on previous epidemiological studies or extrapolated from experience in previous modern outbreaks: SARS, MERS, H1N1 influenza, and include efforts aimed at transmission mitigation, exposure tracing, and improving clinical management [2,6,7]. However, the unprecedented scope of the pandemic necessitated adjustments to nearly all aspects of

* Corresponding author. Department of Surgery, Division of Surgical Oncology Yale University School of Medicine. 310 Cedar Street, FMB 130 New Haven, CT, 06520-8062, USA.
E-mail address: John.Kunstman@yale.edu (J.W. Kunstman).

https://doi.org/10.1016/j.heliyon.2023.e22043
Received 21 December 2021; Received in revised form 29 October 2023; Accepted 2 November 2023
Available online 4 November 2023

medical care, even if unrelated to acute COVID-19 infection. Surgical care was deeply affected by COVID-19. Many healthcare systems in the United States deferred or greatly curtailed elective surgical procedures to facilitate increased inpatient bed availability, preserve personal protective equipment, and minimize the risk of viral transmission during anesthetic management of the airway under the guidance of several governing bodies and surgical societies [8–11]. Secondary and unintended consequences of such policies remain an area of ongoing review. The PREDICT Study, a recent international, longitudinal study reported 4-fold increase in all-cause in-hospital mortality in emergency surgical patients that presented with, or developed, COVID during their hospitalization [12]. The PREDICT study broadly included patients with traumatic, vascular, cardiothoracic, endocrine, orthopedic, and emergency general surgical diagnoses.

The presentation severity, treatment paradigms, and outcomes for emergency general surgery patients with and without COVID infection during the early pandemic compared to pre-pandemic norms remains unknown. Given concerns for continued COVID-19 variant development and additional localized "waves" of this disease and possible future pandemics, strategies to optimize acute surgical care during crisis are urgently needed. Study of both COVID-19 infected and COVID-19 *un*infected patients is required to fully understand the pandemic's effect.

This study focuses on emergency general surgery patients and seeks to examine the presentation, management, and outcomes of patients with acute cholecystitis (AC), regardless of COVID status. Patients were treated at an academic tertiary care center during the early pandemic response and contrasted to a reference cohort of patients with AC prior to the COVID-19 pandemic. The primary aim of this study is to investigate changes in treatment, surgical outcomes and morbidity of patients with AC during the early COVID-19 pandemic. Secondary analysis compares severity of illness at presentation, and sub-group analysis explores time-to-treatment, operative time, and hospital length of stay.

2. Materials and methods

A retrospective analysis of patients treated for acute cholecystitis at an academic tertiary care medical center heavily affected by the COVID-19 pandemic was performed. Institutional Review Board authorization was obtained from the academic medical center, and consent waiver was grant for the presentation of de-identified data. Study cohorts captured patients $\geq$ 18 years of age that were admitted to the hospital with an ICD-10 code indicating acute cholecystitis (K80.*), cholelithiasis (K81.*), or unspecific disorders of the gallbladder (K82.*). The early COVID cohort captured patients between March 12th, 2020–May 12th, 2020, while the reference control cohort included patients admitted between September 12th, 2019–November 12th, 2019. The control cohort was chosen to mirror the length of the study cohort, and the length of follow up data ended prior to the first reported case of COVID in the United States (January 19th, 2020) [13]. The study cohort begins the first full day after COVID was declared a global pandemic by the World Health Organization [14]. The retrospective nature of this study analyzes data from the rapidly evolving early COVID timeframe, before the development of COVID vaccines. Patients were treated at a single large tertiary academic hospital in the Northeastern United States that was inundated with COVID patients during the study period. Determination of need for surgical intervention was at the discretion of the acute care surgery section, and treatment decisions were made prior to now published societal and data-driven guidelines [15,16].

Manual evaluation of each study participant's medical record was performed to verify study inclusion criteria, and to gather patient demographics, comorbidity and illness severity data, clinical course, and 30-day outcome and complication metrics. Demographic data collected consists of patient: age, gender, and self-reported racial identity. Comorbidities accounted for in the Charlson Comorbidity Index (CCI) were captured, and a composite CCI score was calculated for each patient. Severity of acute cholecystitis (AC) was graded using 2018 Tokyo Severity Grading system [17,18].

Abstracted data regarding clinical course included treatment method: cholecystectomy (CCY), percutaneous cholecystostomy (PC), and non-operative management (antibiotics alone or palliative intent). For patients managed with CCY, an additional time-to-treatment analysis was performed to investigate any differences between cohorts in presentation to procedure start time, operative duration, and length of hospital stay. Morbidity was classified by the Clavien-Dindo system [19–21]. Special attention was given to pre-hospitalization COVID status, and COVID status during hospitalization and 30 days following discharge. 30-day readmission data was also captured for all patient groups. Additionally, 2.5 year follow up of data was collected for patients managed non-operatively. Treatment modality was evaluated with a chi-squared test and T-tests were calculated to determine if there were differences within the study and control group regarding outcomes, complications, or time-to-treatment. Statistics were performed in SPSS (IBM Corp.; Armonk, NY, USA).

3. Results

3.1. Demographic data and clinical management

77 patients were evaluated with AC during the study period. The 2019 control cohort included 53 patients and the COVID-19 cohort included 24 patients. Both groups displayed a slight female predominance with the control cohort at 30/53 (56.6 %) and the COVID-19 cohort at 15/24 (62.5 %), $p = 0.63$. The represented ages were similar with the control cohort mean age at 55.1 years, and the COVID-19 cohort at 55.8 years, $p = 0.88$. Body mass index (BMI) for the control cohort ranged from 19.4 to 80.6 with a mean of 31.6 while the COVID-19 cohort ranged from 18.7 to 39.5 with a mean of 28.9, $p = 0.24$. The mean CCI score for the control cohort was 2.89, and for the COVID-19 group it was 2.96, $p = 0.91$. A summary of the demographic data is displayed in Fig. 1A. Self-reported racial identity was captured for each cohort and yielded a similar distribution (Fig. 1B).

Of the 53 patients in the control cohort, 39 (73.6 %) underwent cholecystectomy, 8 (15.1 %) underwent percutaneous cholecystostomy, 4 (7.5 %) were managed with antibiotics alone, and 2 (3.8 %) were managed palliatively. In the 24 patient COVID-19 cohort 15 (62.5 %) underwent cholecystectomy, 4 (16.7 %) underwent PC, 5 (20.8 %) were managed with antibiotics alone, and none were treated with palliative intent.

3.2. Surgical sub-group analysis and outcome data

Of the 53 patients in the control cohort, 2 were managed with palliative intent and removed from the sub-group analysis. A surgical management sub-group analysis was performed, containing 39 patients in the control cohort and 15 patients in the COVID-19 cohort who all received cholecystectomy. Time intervals from presentation to operating room, operative duration, and length of hospitalization were captured. While there was no significant difference in this temporal analysis (Table 1), the COVID-19 cohort trended toward reaching the operating room slightly faster (16.6 vs 17.9 h, $p = 0.70$), had slight shorter operative cases (1.43 vs 1.69 h, $p = 0.36$), and shorter hospital stays (1.67 vs 2.51 days, $p = 0.14$).

Data regarding pulmonary complications, contagion of COVID-19 within 30 days from discharge, significant surgical complication (Clavien-Dindo ≥ 3), and 30-day readmission were similar between groups and captured in Table 1. None of the surgical patients in either cohort suffered mortality within 30 days of discharge. In the COVID-19 cohort no patients were diagnosed with COVID-19 during their hospitalization or within 30 days of discharge.

3.3. Non-surgical sub-group outcome analysis

Patients that were treated with PC or antibiotics alone with curative intent were analyzed in the non-surgical sub-group analysis (Table 1). The control cohort had 12 patients, and the COVID cohort 9 patients. Rates of pulmonary illness was similar between groups, with 3/12 (25 %) in the control cohort and 3/9 (33 %) in the COVID-19 cohort. The control cohort had an unplanned 30-day readmission rate of 8.3 %, while the early COVID cohort had a rate of 11 %. Each cohort also had significant 30-day mortality, 25 % control cohort and 33 % in the COVID-19 cohort. Only 1 of the 9 patients in the 2020 cohort became positive for COVID-19 within thirty days of discharge.

During the 2.5 year follow up from the six non-surgically managed patients of the early COVID cohort who survived beyond the 30-day mark: 2 experienced mortality outside the 30-day study window (one from metastatic cancer and one from medical conditions unrelated to biliary disease), 2 underwent interval cholecystectomy, 1 has been observed without recurrent biliary issues or intervention, and 1 has not undergone cholecystectomy, but has required numerous biliary interventions due to a biliary fistula after undergoing a percutaneous cholecystectomy tube.

A

Presentation Characteristics		2019 Cohort (n = 53)	2020 Cohort (n = 24)	Test of Significance
Demographics	Female Gender (%) Mean Age (years) Mean BMI (BMI Range)	56.6% 55.1 31.6 (19.4 – 80.6)	62.5% 55.8 29.0 (18.7 – 39.5)	.63 .88 .24
Comorbidities	Charlson Comorbidity Index	2.89	2.96	.91
Severity	Tokyo Criteria Score (1 Mild, 2 Moderate, 3 Severe)	1.45	1.63	.22

B

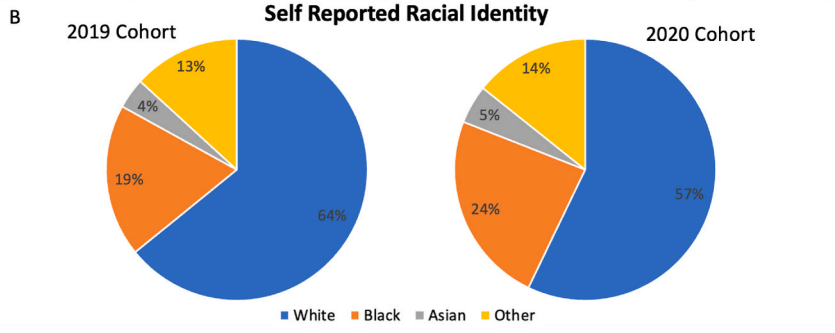


Fig. 1. Baseline characteristic data of study cohorts.

Table 1
Management strategy, complication incidence, and outcome data for each cohort.

All Study Participants		2019 Cohort (n = 53)	2020 Cohort (n = 24)	Test of Significance
Treatment Modality	Cholecystectomy	73.6 %	62.5 %	p = 0.294
	Percutaneous Drainage	15.1 %	16.7 %	
	Antibiotic Therapy Alone	7.5 %	20.8 %	
	Palliative Intent	3.8 %	0 %	
Cholecystectomy Sub-Group Analysis		**2019 Cohort (n = 39)**	**2020 Cohort (n = 15)**	**Test of Significance**
Duration	Presentation to OR (hours)	17.9	16.6	p = 0.70
	Operative Duration (hours)	1.69	1.43	p = 0.36
	Length of Hospitalization (days)	2.51	1.67	p = 0.14
Complications	Pulmonary Complications	0 %	0 %	-
	Subsequent COVID Diagnosis	–	0 %	
	Clavien-Dindo ≥ 3	7.7 %	13.3 %	
	Unplanned 30-day Readmission	12.8 %	13.3 %	
Non-Surgical Sub-Group Analysis (Percutaneous Drainage + Conservative Management)		**2019 Cohort (n = 12)**	**2020 Cohort (n = 9)**	**Test of Significance**
Complications	Pulmonary Pathology*	25 %	33 %	-
	Subsequent COVID Diagnosis	–	11 %	
	Unplanned 30-day Readmission	8.3 %	11 %	
	Mortality within 30 days	25 %	33 %	

3.4. New Haven County COVID-19 incidence

The study center is a tertiary academic hospital in the New Haven, Connecticut that experienced a high burden of community COVID-19 disease during the study timeframe as displayed in Fig. 2. In the weeks following the announcement of COVID-19 as a pandemic, testing was scarce and had a high positivity rate around 5–8% during our study timeframe.

4. Discussion

The COVID-19 pandemic introduced unprecedented challenges to healthcare systems and hospitals across the world. In the early weeks after the global pandemic was declared by the World Health Organization on March 11th, 2020, policies at national and local levels were enacted based on previous pandemic experience and speculative common sense practices. By comparing the presentation, management, and outcomes of patients with a relatively ubiquitous surgical disease (acute cholecystitis) this study aims to shed light onto a hospital's ability to continue routine surgical care safely during COVID-19 crisis management.

At a Northeastern, US hospital this study was conducted in an epicenter of early COVID disease, and the data presented during the COVID-19 study timeframe accrued when little was known about the disease and when both testing and resources were scarce. This combination of factors captures the extreme hardships encountered and offers observation into epidemiology of acute cholecystitis and the unintended consequences of enacted anti-contagion policies.

Our study reports a striking decrease of admitted patients with AC during the 2020 COVID timeframe (24) as compared to the control cohort (53). Potential reasons for this finding may be a genuine decrease in cholecystitis incidence in the community, possibly due to avoidance of aggravating behavior, or hesitancy to seek medical treatment leading to COVID exposure during active national

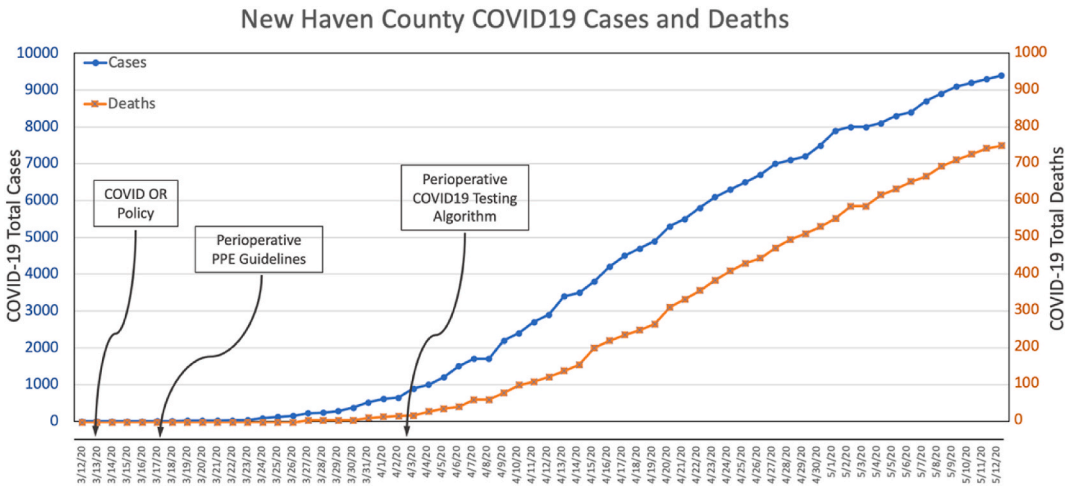


Fig. 2. A timeline of COVID cases, deaths, and hospital policies implementations.

social distancing policies. Interestingly, this did not result in more severe AC in those cases that were evaluated, as the Tokyo Severity Score was similar between cohorts.

Once patients were admitted with AC, fewer patients underwent surgical management in the 2020 COVID timeframe with more patients undergoing non-operative management ($p = 0.294$). Of those, a relatively consistent fraction of patients underwent PC with the increase consisting of patients undergoing medical management alone. Despite this trend toward less operative management of AC in the 2020 COVID cohort, there remains low rates of complication and 30-day readmission. The PREDICT study reported a significant increase in in-hospital mortality for patients diagnosed with COVID [12]. Our study's focus on patients with AC yielded only one COVID-positive patient who died within 30 days of their AC diagnosis, and our analysis is instead focused on treatment decisions and how patients progressed through their treatment. At our institution, careful patient selection for surgery in the setting of adherence to national guidelines for safe employment of general anesthesia and operative intervention allowed judicious use of scare resources without a detriment to patient outcome.

In the surgical sub-group analysis, these findings demonstrates that policies designed to mitigate risks of iatrogenic COVID transmission did not have a deleterious effect on operative room access. At our institution, specially designated operating rooms for COVID-positive or COVID-unknown status patients, novel personal protective equipment protocols for staff and patients, and pre-operative COVID-19 testing did not result in delays to operative therapy in patients with AC. Moreover, there were no differences in duration of surgery or length of stay. Both trended lower in the COVID cohort; particularly notable is the mean length of stay was one-third shorter for patients in the COVID era. Although not reaching statistical significance, we surmise that this was due to the increased emphasis on bed availability in the COVID era.

While the limitations of retrospective data analysis are inherent in this study, the two cohorts were well-matched from a demographic and disease standpoint. Whether the findings here can be applied to surgical problems beyond AC is unknown, although extrapolation to other general surgical diseases of the abdomen seems appropriate. In addition, this study was performed at a tertiary care center which may also limit the extent of its generalization. However, our center was an early and high-volume referral center for patients with COVID. Crucially, no patients developed COVID infection during the duration of their hospitalization, suggesting that anti-contagion and isolation policies were effective despite this being a very early stage in the pandemic in the United States. Similar surgical outcomes observed during the COVID era in this study, indicate that AC can be safely and effectively managed through periods of high COVID prevalence in a community. This finding remains important as COVID variants continue to develop, and data has emerged that variants display immune-evasion necessitating continued vaccine development and booster administration to the general population [22–24]. Additionally, as countries prepare to shift away from zero COVID policies, regional hot spots are at risk of developing [25,26].

5. Conclusions

At an academic tertiary care hospital, patients with acute cholecystitis requiring surgical intervention during the early phases of the COVID-19 pandemic were able to safely and efficiently receive surgical care. Implementation of anti-contagion and isolation policies designed to limit in-hospital COVID-19 spread did not negatively affect timeliness of undergoing definitive surgical management or patient outcomes. This study suggests that management of acute cholecystitis during the COVID-19 pandemic was safe and effective despite the widespread stresses to the healthcare system.

(A) Data regarding the demographics, comorbidity status, and acute cholecystitis severity of each cohort was captured and there were no significant differences between the two cohorts. (B) Self-reported racial identity data was similar between cohorts.

Management decisions for each cohort are contrasted, and a trend toward more conservative management is noted in the early COVID cohort. Sub-group complication and outcome analysis was performed for the surgical and non-surgical subgroups. A time-to-treatment analysis was additionally performed on the surgical cohort. * Pulmonary pathology included: the in-hospital diagnosis of pneumonia, use of a ventilator, or pulmonary embolism.

A timeline reporting the COVID cases and death in New Haven County. Specific notations indicate when COVID-specific policies were implemented.

Ethics statement

Yale University Human Research Protection Program Institutional Review Boards.
Approved IRB Protocol ID: 200,002,876.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability statement

Data presented in this manuscript has not been deposited into a publicly available repository, as it was not covered in the original study IRB.

CRediT authorship contribution statement

Nicholas V. Peters: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Rick O'Connor:** Writing – review & editing, Investigation, Formal analysis, Data curation. **Bishwajit Bhattacharya:** Writing – review & editing, Writing – original draft, Supervision, Investigation, Formal analysis, Conceptualization. **John W. Kunstman:** Writing – review & editing, Writing – original draft, Supervision, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Yale University School of Medicine.
Yale New Haven Hospital – Department of Surgery.

References

[1] Z. Wu, J.M. McGoogan, Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese center for disease control and prevention, JAMA 323 (13) (2020) 1239–1242.
[2] S. Hsiang, D. Allen, S. Annan-Phan, et al., The effect of large-scale anti-contagion policies on the COVID-19 pandemic, Nature 584 (7820) (2020) 262–267.
[3] M.L. Ranney, V. Griffeth, A.K. Jha, Critical supply shortages - the need for ventilators and personal protective equipment during the covid-19 pandemic, N. Engl. J. Med. 382 (18) (2020) e41.
[4] A.K. Mph, Ventilator Stockpiling and Availability in the US, 2021. https://www.centerforhealthsecurity.org/resources/COVID-19/COVID-19-fact-sheets/200214-VentilatorAvailability-factsheet.pdf. Published 2020. Updated 9/3/2020. Accessed 5/17/2021.
[5] H. Xu, O. Intrator, J.R. Bowblis, Shortages of staff in nursing homes during the COVID-19 pandemic: what are the driving factors? J. Am. Med. Dir. Assoc. 21 (10) (2020) 1371–1377.
[6] M.S. Kim, M.H. An, W.J. Kim, T.H. Hwang, Comparative efficacy and safety of pharmacological interventions for the treatment of COVID-19: a systematic review and network meta-analysis, PLoS Med. 17 (12) (2020), e1003501.
[7] I.M. Tleyjeh, Z. Kashour, M. Damlaj, et al., Efficacy and safety of tocilizumab in COVID-19 patients: a living systematic review and meta-analysis, Clin. Microbiol. Infect. 27 (2) (2021) 215–227.
[8] M.E. Brindle, A. Gawande, Managing COVID-19 in surgical systems, Ann. Surg. 272 (1) (2020) e1–e2.
[9] B. De Simone, E. Chouillard, S. Di Saverio, et al., Emergency surgery during the COVID-19 pandemic: what you need to know for practice, Ann. R. Coll. Surg. Engl. 102 (5) (2020) 323–332.
[10] Services CfMaM. Non-Emergent, Elective Medical Services, and Treatment Recommendations, 2021. https://www.cms.gov/files/document/cms-non-emergent-elective-medical-recommendations.pdf. Published 2020. Updated 4/7/2020. Accessed 5/28/2021.
[11] CfD. Control, Framework for Healthcare Systems Providing Non-COVID-19 Clinical Care during the COVID-19 Pandemic, 2021. https://www.cdc.gov/coronavirus/2019-ncov/hcp/framework-non-COVID-care.html. Published 2020. Updated 6/30/2020. Accessed 5/28/2020.
[12] J.W. Beatty, J.M. Clarke, V. Sounderajah, et al., Impact of the COVID-19 pandemic on emergency adult surgical patients and surgical services, An International Multi-Center Cohort Study and Department Survey, Ann Surg 274 (6) (2021) 904–912.
[13] M.L. Holshue, C. DeBolt, S. Lindquist, et al., First case of 2019 novel coronavirus in the United States, N. Engl. J. Med. 382 (10) (2020) 929–936.
[14] W.D. General, WHO Director-General's Opening Remarks at the Media Briefing on COVID-19 - 11 March 2020, 2021. https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19—11-march-2020. Published 2019. Accessed 5/17/2021.
[15] V.N. Prachand, R. Milner, P. Angelos, et al., Medically necessary, time-sensitive procedures: scoring system to ethically and efficiently manage resource scarcity and provider risk during the COVID-19 pandemic, J. Am. Coll. Surg. 231 (2) (2020) 281–288.
[16] Surgeons Aco, COVID-19 Guidelines for Triage of Emergency General Surgery Patients, 2021. https://www.facs.org/covid-19/clinical-guidance/elective-case/emergency-surgery. Published 2020. Updated 12/8/2020. Accessed 5/10/2021.
[17] M. Yokoe, J. Hata, T. Takada, et al., Tokyo Guidelines 2018: diagnostic criteria and severity grading of acute cholecystitis (with videos), J Hepatobiliary Pancreat Sci 25 (1) (2018) 41–54.
[18] M. Yokoe, T. Takada, S.M. Strasberg, et al., TG13 diagnostic criteria and severity grading of acute cholecystitis (with videos), J Hepatobiliary Pancreat Sci 20 (1) (2013) 35–46.
[19] M. Bolliger, J.A. Kroehnert, F. Molineus, D. Kandioler, M. Schindl, P. Riss, Experiences with the standardized classification of surgical complications (Clavien-Dindo) in general surgery patients, Eur. Surg. 50 (6) (2018) 256–261.
[20] P.A. Clavien, J.R. Sanabria, S.M. Strasberg, Proposed classification of complications of surgery with examples of utility in cholecystectomy, Surgery 111 (5) (1992) 518–526.
[21] D. Dindo, N. Demartines, P.A. Clavien, Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey, Ann. Surg. 240 (2) (2004) 205–213.
[22] L. Forchette, W. Sebastian, T. Liu, A comprehensive review of COVID-19 virology, vaccines, variants, and therapeutics, Curr Med Sci 41 (6) (2021) 1037–1051.
[23] Y. Kherabi, O. Launay, L.B. Luong Nguyen, COVID-19 vaccines against omicron variant: real-world data on effectiveness, Viruses 14 (10) (2022).
[24] S.A. Madhi, V. Baillie, C.L. Cutland, et al., Efficacy of the ChAdOx1 nCoV-19 covid-19 vaccine against the B.1.351 variant, N. Engl. J. Med. 384 (20) (2021) 1885–1898.
[25] W. Bai, S. Sha, T. Cheung, Z. Su, T. Jackson, Y.T. Xiang, Optimizing the dynamic zero-COVID policy in China, Int. J. Biol. Sci. 18 (14) (2022) 5314–5316.
[26] A. Brault, C. Tran-Kiem, C. Couteaux, et al., Modelling the end of a Zero-COVID strategy using nirmatrelvir/ritonavir, vaccination and NPIs in Wallis and Futuna, Lancet Reg Health West Pac 30 (2023), 100634.