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high-risk groups that have more complications and higher mortality in COVID-19 coincide with groups that have a high incidence of vitamin D deficiency. We believe that vitamin D deficiency might be one of the important risk factors for COVID-19 complications and higher mortality.

Studies of vitamin D replacement have shown that vitamin D ameliorates innate immunity (the immediate response of macrophages to invading viruses and bacteria in the mucous membranes),<sup>2</sup> thereby reducing the incidence and severity of acute respiratory infections.<sup>3</sup> This effect requires a sufficient serum level of 25(OH)D3 being crucial for macrophages to activate it into hormone D (calcitriol), which activates genes for the synthesis of antimicrobial factors destroying viruses (such as SARS-CoV-2), fungi, and bacteria.<sup>2</sup> Also, vitamin D modulates the cellular immune response and, as expected, attenuates the cytokine storm,<sup>4</sup> the event so fatal in SARS-CoV-2–induced pneumonia. Therefore, we suggest it would be reasonable to supplement vitamin D in subpopulations at risk of vitamin D deficiency and unfavorable COVID-19 outcomes, as well as in individuals already infected with SARS-CoV-2 to achieve optimal 25(OH)D3 concentrations as quickly as possible.

It is challenging to conduct evidence-based medicine in cases such as the COVID-19 pandemic. To the best of our knowledge, there are no data on the effects of vitamin D in SARS-CoV-2 infection; then again, there are reliable data on the beneficial effects of cholecalciferol in attenuating viral respiratory infections in people with low levels of vitamin D. The European Centre for Disease Prevention and Control makes this argument and encourages health care professionals to take actions that are logical in their own

right, based on previously known findings in related fields: “Public health authorities should recognize that extra-scientific factors (e.g. feasibility of implementing scientific advice, time pressure, socio-political factors, institutional factors, economic interests, pressure from neighboring countries etc.) are inherent to the decision-making process. These factors will also influence the implementation of any proposed response measures. Decisions should therefore always be evidence informed, but they will very rarely be purely evidence based.”<sup>5</sup> In Slovenia, in view of COVID-19 pandemic, medical doctors were urgently advised by leading experts to supplement vitamin D in high-risk and fragile individuals and in COVID-19 patients. With this letter to the editor we address the broader medical community to urgently consider vitamin D supplementation in high-risk patients for adverse COVID-19 outcomes.

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1. Kennel KA, Drake MT, Hurley DL. Vitamin D deficiency in adults: when to test and how to treat. *Mayo Clin Proc.* 2010;85(8):752-758.

- Zdrengea MT, Makrinioti H, Bagacean C, Bush A, Johnston SL, Stanciu LA. Vitamin D modulation of innate immune responses to respiratory viral infections. *Rev Med Virol.* 2017;27(1). <https://doi.org/10.1002/rmv.1909>. Epub 2016 Oct 7.
- Martineau AR, Jolliffe DA, Hooper RL, et al. Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. *BMJ.* 2017; 15:356:i6583.
- Khoo AL, Chai LY, Koenen HJ, et al. Regulation of cytokine responses by seasonality of vitamin D status in healthy individuals. *Clin Exp Immunol.* 2011; 164(1):72-79.
- European Centre for Disease Prevention and Control. *Considerations relating to social distancing measures in response to COVID-19 — second update.* Stockholm: ECDC; 2020. <https://www.ecdc.europa.eu/sites/default/files/documents/covid-19-social-distancing-measuresg-guide-second-update.pdf>. Accessed April 17, 2020.

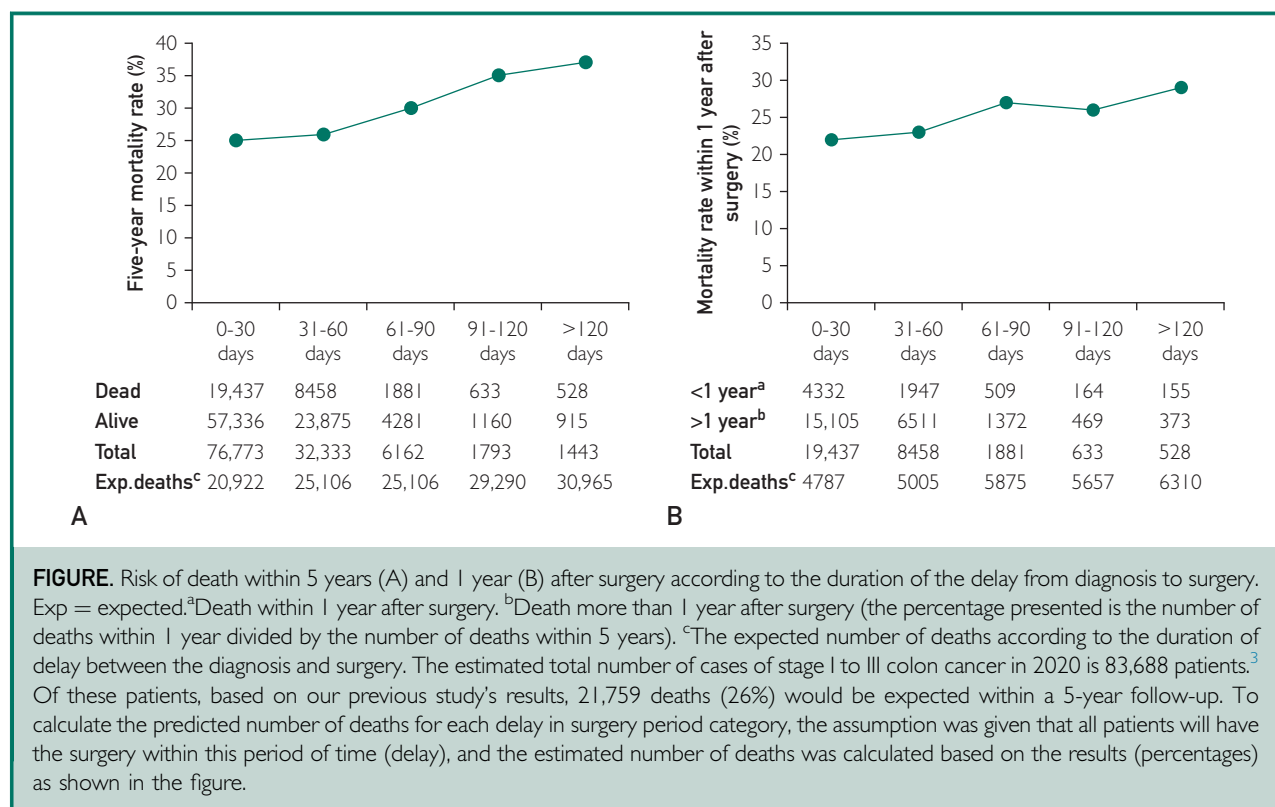
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## How Many Lives Will Delay of Colon Cancer Surgery Cost During the COVID-19 Pandemic? An Analysis Based on the US National Cancer Database



**To the Editor:** By May 13, 2020, 1,342,594 cases of coronavirus disease (COVID-19) had been confirmed in the United States.<sup>1</sup> Of these patients, 80,820 (6%) had died.<sup>1</sup> This rapid viral spread, unencumbered by an effective treatment or vaccine, required wise health care resource utilization decisions. Consequently, many centers throughout the world have decided to delay elective surgical procedures including those for cancer to avoid health care system exhaustion.<sup>2</sup>

Surgical management of colon cancers is considered the cornerstone of treatment, especially in early-stage disease.<sup>3,4</sup> Our team at Mayo Clinic derived results based on the American College of Surgeons National Cancer Database, which concluded that delaying elective surgery for patients with stage I



to III colon cancer was independently associated with the decrease in the 5-year overall survival.<sup>5</sup> Therefore, we have attempted to place into context the potential impact of delay of surgical treatment for patients with colon cancer in the setting of the COVID-19 pandemic.

Within our previous series,<sup>5</sup> 30,937 deaths (26%) occurred among 118,504 patients with colon cancer during a 5-year follow-up. Delaying the surgical resection for patients with stage I to III colon cancer was associated with an increase in the mortality rate within the 5 years of follow-up (25% mortality rate when surgery was performed within 1 month of diagnosis vs 37% after a 4-month delay). This increase in death from cancer was already apparent within the first year (Figure), highlighting the urgency and impact of our nation's health care decisions.

In the United States, we expect to have 104,610 new cases of colon cancer in 2020 with about 83,688 patients having stage I to III colon cancer.<sup>3</sup> This incidence will result in 20,922 (25%) expected deaths within 5 years of surgery if performed within 30 days of diagnosis (Figure). Unfortunately, if colon cancer surgery is delayed for more than 4 months, it has the potential to result in the deaths of 30,965 within the same 5-year period. This potential tragic outcome may result in an additional loss of 10,043 Americans over 5 years (Figure). This model may be an underestimate, as some patients may die before ever undergoing surgical treatment and are not counted. Moreover, this estimate only represents the human tragedy for colon cancer, as the impact of all cancer would be expected to be much

larger. Alternative assumptions according to the period of delay in surgery are presented in the Figure.

Therefore, political and health care leaders must recognize the potential negative impacts on current patients as they address the pandemic before us. Alternative treatments (chemotherapy, immunotherapy, radiotherapy), a national network that would enable referral of patients for surgery in less impacted cities, and screening patients before surgery must be considered to reduce this potential increase in mortality due to the delay in surgical treatment. Furthermore, patients with cancer represent a more vulnerable population and appear to have a higher rate of severe complications after infection with COVID-19. This dilemma, along with many other considerations, puts into focus the importance of decision making

regarding the optimal choice for this vulnerable population.

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- American College of Surgeons. COVID-19: elective case triage guidelines for surgical care. American College of Surgeons website. <https://www.facs.org/covid-19/clinical-guidance/elective-case>. Published March 24, 2020. Accessed on March 31, 2020.
- Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin*. 2020;70(1):7-30.
- Benson AB, Venook AP, Al-Hawary MM, et al. NCCN guidelines insights: colon cancer, version 2. 2018. *J Natl Compr Canc Netw*. 2018;16(4):359-369.
- Grass F, Behm KT, Duchalais E, et al. Impact of delay to surgery on survival in stage I-III colon cancer. *Eur J Surg Oncol*. 2020;46(3):455-461.

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## Medication Shortages: A Matter of National Security—Time for Action



**To the Editor:** As noted by Choo and Rajkumar<sup>1</sup> in the June 2020 issue of *Mayo Clinic Proceedings*, the COVID-19 (coronavirus disease 19) pandemic has exposed extreme vulnerabilities in our nation's drug supply chain. The fragility of the drug supply chain was not created overnight and has been brewing for over a decade. Frequent generic drug shortages and quality deficiencies are compromising standard of care, producing waste, and increasing costs. For example, antibiotic shortages contribute to

resistance, when clinicians are forced to use broad-spectrum agents. Today, 80% of active product ingredient (API) manufacturers are located overseas,<sup>2</sup> with the majority being obtained from India and China. India, a large manufacturer of finished products, obtains 70% of APIs from China.<sup>3</sup> China has a virtual monopoly on the APIs required to make critical drugs such as antibiotics, antihypertensives, and many others. Although the United States remains a global leader in drug discovery, we have almost completely transitioned manufacturing abilities to overseas because of lower production and labor costs. The United States' overreliance on importing APIs from overseas has created a devastating impact on our public health with a potential for catastrophic events in the event of a war, trade conflict, or pandemic such as COVID-19 and impacting our national security. As expected, the United States is waiting in line with every other country for essential drugs during the current pandemic.

Although there are no easy or fast solutions to this problem, we must act now. In addition to Choo and Rajkumar's recommendations, the following steps may be considered with the ultimate goal of domestic manufacturing of most of the essential lifesaving drugs to protect our patients from harm.

- Designate the pharmaceutical industry as a high-priority infrastructure critical to national security (like the aviation and energy sectors) to allow the federal government to coordinate efforts during shortages or national crises.
- Develop an essential national security drug supply list that includes medications for which a supply interruption could cause an immediate risk to public health.

- Create a national agency to monitor, plan, and identify potential manufacturers in the event of a shortage.
- Manufacture products in multiple locations to protect the supply chain in the event of a natural disaster or other threats.
- Strengthen federal oversight of manufacturers to ensure the highest product integrity and require manufacturers to provide transparency related to source of APIs and quality issues.
- Develop a partnership between the private and public sectors acting as a united cohort to uncover incentives to drive actions to ensure domestic production of essential drugs.
- Require manufacturers to report to the US Food and Drug Administration (FDA) immediately on discovery of an interruption, disclosing the reason and the expected time to resolution.
- Create a national database for tracking of essential drug supplies and use predictive analytics to identify surge, production problems, and future shortages.
- Allow outsourced 503B compounds to prepare drugs in short supply.
- Allow the FDA to prioritize and expedite generic drug approvals.
- Provide adequate FDA resources to allow frequent inspection of overseas facilities to ensure product integrity and quality.

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