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Mortality of Laryngeal Cancer before and during the COVID-19 Pandemic

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Abstract: (1) Background: The interplay between coronavirus disease 2019 (COVID-19) and laryngeal cancer represents a substantial challenge for both patients and healthcare. To garner information on recent mortality data for laryngeal cancer, including during the COVID-19 pandemic, we analyzed real-world data from the US Centers for Disease Control and Prevention (CDC). (2) Methods: We searched the CDC WONDER online database 2018–2022 using the ICD-10 code for laryngeal cancer (C32; malignant neoplasm of the larynx). We also performed a sub-analysis between genders and across ten-year age groups. The data were analyzed with one-way analysis of variance (ANOVA) and Tukey's post hoc test. (3) Results: The trend of age-adjusted mortality ×100,000 did not change significantly between the years 2018 and 2022 ($p = 0.553$). Males had higher age-adjusted mortality rates (M/F ratios between 4.6 and 5.0), but no significant variation was found in both genders (males: $p = 0.676$; females: $p = 0.596$). Although the mortality rate remained unchanged in people aged 35–84 years, the variation reached statistical significance in those aged 85 or older ($p = 0.004$), displaying a significant increase in 2021 compared to 2018 ($p = 0.006$) and 2019 ($p = 0.039$). (4) Conclusions: The impact of the COVID-19 pandemic on mortality for laryngeal cancer seems to be relatively modest in the general US population. Nevertheless, closer attention must be paid to older people, for whom the unfavorable consequences of misdiagnosis or mistreatment of this and other types of cancers can be exacerbated.

Keywords: mortality; COVID-19; laryngeal cancer; larynx cancer

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1. Introduction

The larynx, which is located in the throat over the trachea, is a vital structure in the human body as it plays an important role in breathing, swallowing, and the production of speech sounds. The pathologies of this anatomical site range from benign conditions such as infections and/or inflammation (i.e., laryngitis), benign nodules and/or polyps, to life-threatening pathologies, the most threatening of which is laryngeal cancer. These malignancies can originate from any part of the larynx, including the vocal cords, epiglottis, arytenoid cartilage, and other surrounding tissues [1,2].

Among the different types of laryngeal cancer, squamous cell carcinoma, which usually arises from the flat, thin cells lining the inside of the larynx, is the most common form and accounts for the vast majority (almost 90%) of malignancies in this anatomical site, followed by less common types of cancers such as adenocarcinoma (which usually arises from the glandular cells of the larynx) and sarcomas (which develop in the connective tissue of the larynx, such as muscle, cartilage, or fat) [3]. Laryngeal cancers can also be classified according to anatomical site (i.e., supraglottic, glottic, and subglottic), and are characterized by different pathophysiology and often require different therapeutic management [3].

The main risk factors for laryngeal cancer include cigarette smoking, tobacco chewing, heavy alcohol consumption, male gender, advanced age, exposure to certain chemicals (like asbestos, nickel, sulfuric acid fumes, formaldehyde, and isopropyl alcohol), local infections (especially human papillomavirus [HPV] type 16), and gastroesophageal reflux disease, among others [3].

The most common symptoms include hoarseness or changes in voice quality lasting longer than 2 to 3 weeks, persistent sore throat or cough, difficulty swallowing, earache, the appearance of lumps or masses in the throat, difficulty breathing, and even weight loss [3]. The diagnosis of laryngeal cancer usually involves a combination of physical examination, imaging studies (such as computed tomography [CT] scans or magnetic resonance imaging [MRI]), and local biopsy of the mass [4]. The prognosis of laryngeal cancer depends on several factors, including the stage of cancer, the patient's health status, early diagnosis, and the effectiveness of treatment, because it is generally assumed that early detection and treatment are associated with better outcomes. Recent data show that the 5-year survival rate of laryngeal cancer is between 64 and 74% [5].

Several lines of evidence suggest that the interplay between coronavirus disease 2019 (COVID-19) and laryngeal cancer may be considered a substantial challenge for patients and healthcare. For example, individuals with early forms of cancer may have developed a weaker immune response against the malignancy due to the direct effect of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on the immune system [6]. Additional factors include the global disruptions in cancer screening, diagnosis, and treatment that may have been associated with a significant delay in diagnosis and treatment [7]; also, another factor is the increased risk of respiratory complications since laryngeal cancers impair breathing and respiratory function, conditions that could be aggravated by SARS-CoV-2 infection [8]. Therefore, to garner recent information on mortality of laryngeal cancer, especially during the last few years (some of which were dominated by the COVID-19 pandemic), we perform an analysis of real-world data made available by the US Centers for Disease Control and Prevention (CDC).

2. Materials and Methods

2.1. Database Search

We accessed the last updated version of the CDC WONDER online database, which reports mortality data between the years 2018 and 2022 for the US resident population [9]. This information is derived from demographic information and death certificates reporting a unique cause of death. The original search was made using "year" as the first variable, combined with the ICD-10 code for laryngeal cancer as the second variable (ICD-10: C32; malignant neoplasm of the larynx). The search was then expanded with a sub-analysis of the mortality of laryngeal cancer between genders (males and females) and across ten-year age groups, as available in the database for this type of cancer (35–44, 45–54, 55–64, 65–74, 75–84, and +85 years). The final output of the database search includes the total number of deaths for specific ICD-10 codes, the crude or age-adjusted mortality rate $\times$ 100,000 (i.e., the deaths in age group $\div$ estimated population of that age group $\times$ 100,000) with 95% confidence interval (95%CI) or standard error (SE).

2.2. Statistical Analysis

The data were analyzed with one-way analysis of variance (ANOVA) and Tukey's post hoc test (StatPages, Interactive Statistical Calculation). Statistical significance was set at $p < 0.05$. The study was conducted in accordance with the Declaration of Helsinki and within the terms defined by the local legislation. Since this analysis was based on retrospective data from the freely searchable WONDER anonymized database, no informed consent or ethical committee approval were necessary.

3. Results

Our main findings are summarized in Figure 1 and Table 1.

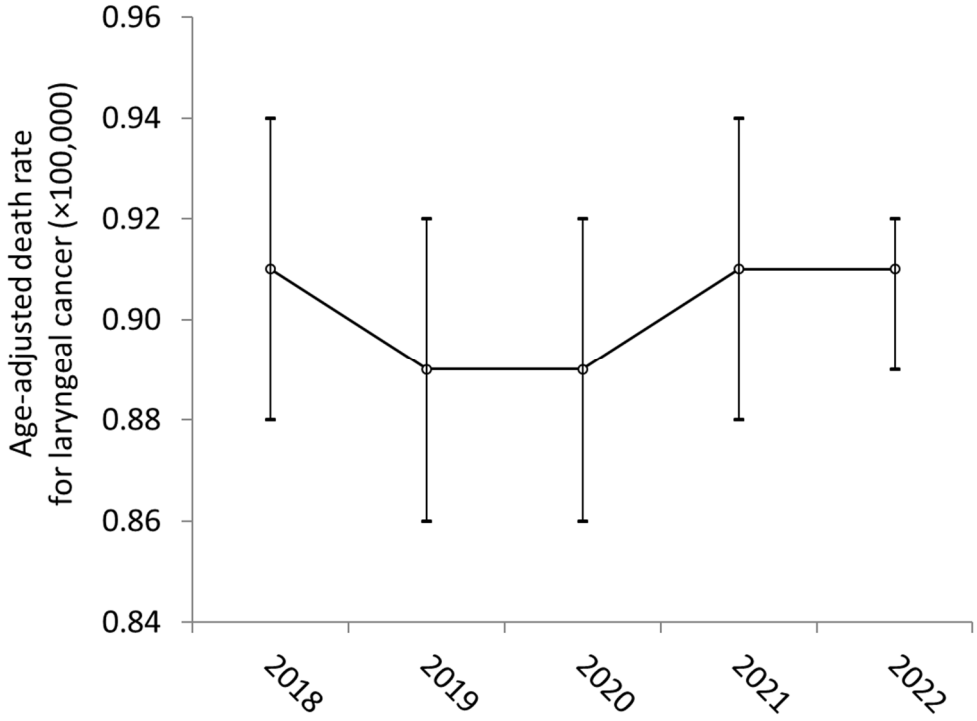

Figure 1. Age-adjusted death rate for laryngeal cancer (95% confidence interval; 95%CI) in the US during the period 2018–2022. Data are expressed as crude or age-adjusted death rate × 100,000.

Table 1. Mortality for laryngeal cancer (95% confidence interval; 95%CI) in the US during the period 2018–2022. Data are expressed as crude or age-adjusted death rate × 100,000.

Years	2018	2019	2020	2021	2022
Overall	0.91 (0.84–0.94)	0.89 (0.86–0.92)	0.89 (0.86–0.92)	0.91 (0.88–0.94)	0.91 (0.89–0.92)
Gender					
- Males	1.60 (1.54–1.66)	1.58 (1.64–1.52)	1.56 (1.62–1.51)	1.61 (1.67–1.55)	1.56 (1.61–1.50)
- Females	0.34 (0.31–0.36)	0.34 (0.31–0.36)	0.33 (0.31–0.35)	0.32 (0.34–0.30)	0.33 (0.31–0.35)
- Ratio (M/F)	4.7	4.6	4.7	5.0	4.7
Age (years)					
- 35–44	0.05 (0.03–0.08)	0.04 (0.02–0.06)	0.07 (0.04–0.10)	0.05 (0.03–0.08)	0.06 (0.04–0.08)
- 45–54	0.65 (0.57–0.73)	0.58 (0.51–0.66)	0.59 (0.52–0.67)	0.60 (0.53–0.68)	0.50 (0.43–0.57)
- 55–64	2.58 (2.43–2.74)	2.51 (2.36–2.66)	2.37 (2.22–2.52)	2.35 (2.20–2.49)	2.29 (2.15–2.44)
- 65–74	4.15 (3.92–4.38)	4.11 (3.89–4.33)	3.91 (3.69–4.12)	3.98 (3.77–4.19)	4.21 (3.99–4.43)
- 75–84	5.01 (4.66–5.37)	5.10 (4.75–5.45)	5.03 (4.68–5.37)	5.29 (4.94–5.65)	5.31 (4.97–5.66)
- ≥85	5.39 (4.83–5.96)	5.68 (5.10–6.25)	6.46 (5.85–7.07)	6.91 (6.24–7.58)	5.92 (5.33–6.51)

The age-adjusted mortality rate × 100,000 for laryngeal cancer was 0.91 (95%CI, 0.84–0.94) in 2018; 0.89 (95%CI, 0.86–0.92) in 2019; 0.89 (95%CI, 0.86–0.92) in 2020; 0.91 (95%CI, 0.88–0.94) in 2021; and 0.91 (95%CI, 0.89–0.92) in 2022. This trend was not statistically significant according to a one-way ANOVA (f = 0.757; $p = 0.553$). Tukey's post hoc test revealed no statistically significant differences across multiple comparisons of different years throughout the study period (all $p \geq 0.791$).

Table 1 and Figure 2 show the gender- and age-specific mortality trends for laryngeal cancer between 2018 and 2022. Males had consistently higher age-adjusted mortality rates than females, with M/F ratios ranging between 4.6 and 5.0 between 2018 and 2022.

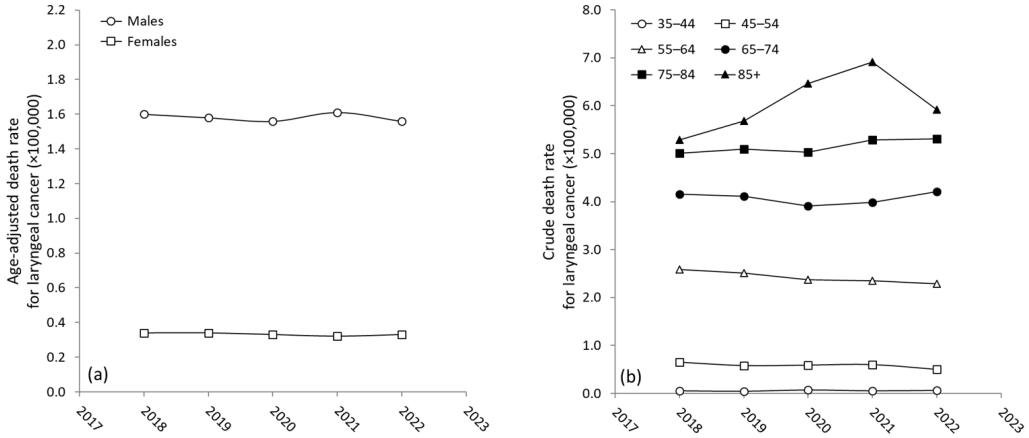

Figure 2. Age-adjusted death rate for laryngeal cancer (95% confidence interval; 95%CI) in the US during the period 2018–2022 (**a**) between genders and (**b**) across age classes. Data are expressed as crude or age-adjusted death rate ×100,000.

The one-way ANOVA revealed no significant differences in mortality trends in both genders before and during the COVID-19 pandemic (males: f = 0.58, p = 0.676; females: f = 0.694, p = 0.596). Nonetheless, there were some differences in the age-specific trend of laryngeal cancer mortality between 2018 and 2022 (Table 2).

Table 2. Significance of trends for mortality for laryngeal cancer in the US during the period 2018–2022 in different age classes by one-way analysis of variance (ANOVA).

	f-Value	***p*-Value**
All age classes	0.76	0.553
35–44 years	1.24	0.300
45–54 years	1.72	0.142
55–64 years	2.63	0.052
65–74 years	1.23	0.269
75–84 years	0.668	0.614
≥85 years	3.90	0.004

As predictable, the mortality for laryngeal cancer increased in parallel with the aging of the population. Although the values remained mostly unchanged or only showed minor and non-statistically significant variations in people aged 35–44 years (f = 1.24; p = 0.300; no significant differences among the different years according to Tukey's post hoc test); 45–54 years (f = 1.72; p = 0.142; no significant differences among the different years according to Tukey's post hoc test); 55–64 years (f = 2.63; p = 0.052; no significant differences among the different years according to Tukey's post hoc test); 65–74 years (f = 1.23; p = 0.296; no significant differences among the different years according to Tukey's post hoc test); and 75–84 years (f = 0.668; p = 0.614; no significant differences among the different years according to Tukey's post hoc test), significant variation was found in the older age group. Specifically, in people aged 85 years or older, which represent around 13% of the overall US population, the 2018–2022 trend reached statistical significance using one-way ANOVA (f = 3.90; p = 0.004), displaying a significant increase in mortality rate in 2021 compared to 2018 (p = 0.006) and 2019 (p = 0.039), respectively (Figure 2).

4. Discussion

Laryngeal cancer accounts for 30–40% of all head and neck malignancies and continues to impose a major burden on healthcare and society due to its significant impact on

quality of life, morbidity, and mortality. Although it has previously been demonstrated that mortality from this malignancy has declined in many developed countries in recent decades [10,11], COVID-19 may have reversed this positive trend for a variety of reasons other than for the direct interplay of SARS-CoV-2 with the host immune system, including disruption of cancer screening and diagnosis, deferred or even discontinued treatments, surveillance and follow-up, and impeded access to clinical trials and innovative therapies [12]. The most obvious consequence is the delayed detection of some cancers and the diagnosis of some malignancies at a more advanced stage than in the pre-pandemic period, which may be attributable to several factors such as fear of infection, healthcare system strain, the disruption of diagnostic pathways, and a backlog of cases [13,14].

Regarding laryngeal cancer, the results of our retrospective analysis of real-world data provided by the US CDC show that the cumulative mortality for this malignancy has not changed significantly during the COVID-19 pandemic, as the age-adjusted death rate has always remained between 0.89–0.91 × 100,000 from 2018 to 2022. There were also no significant variations in the mortality rate for laryngeal cancer between the sexes or in most age groups. However, our analysis also shows that the mortality rate for this cancer has exhibited a significant increase in 2021 in people aged 85 years or older, following a trend that already saw a non-significant increase in 2020. Thereafter, in 2022, the mortality rate in this older population returned to values comparable to those of 2018–2019, reflecting the lower virulence of SARS-CoV-2, the higher level of herd immunity developed over time (either naturally or through vaccination), and the release of most measures of social restriction (i.e., lockdowns, curfews, quarantines, isolation, etc.) with eased access to care [15]. We recognize that the mortality data for laryngeal cancer only provide a general representation of events during the COVID-19 pandemic, but this is the only information available in the CDC Wonder database. Additional analyses could be conducted to consider other types of data (i.e., health discharge records from administrative health databases) that allow for a more comprehensive evaluation of the impact of the pandemic on this and other types of cancers.

5. Conclusions

In conclusion, our analysis of real-world data on laryngeal cancer mortality suggests that the impact of the COVID-19 pandemic may have been relatively modest in the general US population, except for the population aged 85 years or older. Therefore, one important aspect that has emerged for the future is the need to devote more efforts to the health of older people during similar global tragedies, as the biological consequences of misdiagnosis or mistreating malignancies, including laryngeal cancer, can be enormously amplified in this highly vulnerable part of the general population. Further studies are needed to determine whether the medium- and long-term mortality from laryngeal cancer will be impacted by the COVID-19 pandemic.

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Informed Consent Statement: Not applicable.

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References

1. Parker, D.A.; Robin, P.E. Investigation of laryngeal pathology: A review of diagnostic techniques. *Clin. Otolaryngol. Allied Sci.* **1989**, *14*, 79–89. [CrossRef] [PubMed]
2. Adriaansen, A.; Van Lierde, K.; Meerschman, I.; Claeys, S.; D'haeseleer, E. The Occurrence of Laryngeal Pathologies in a Treatment-Seeking Pediatric Population. *J. Voice* **2023**. [CrossRef] [PubMed]
3. Koroulakis, A.; Agarwal, M. Laryngeal Cancer. In *StatPearls*; StatPearls Publishing: Treasure Island, FL, USA, 2024. Available online: https://www.ncbi.nlm.nih.gov/books/NBK526076/ (accessed on 9 May 2024).
4. Itamura, K.; Hsue, V.B.; Barbu, A.M.; Chen, M.M. Diagnostic Assessment (Imaging) and Staging of Laryngeal Cancer. *Otolaryngol. Clin. N. Am.* **2023**, *56*, 215–231. [CrossRef] [PubMed]
5. Siegel, R.L.; Miller, K.D.; Jemal, A. Cancer statistics, 2020. *CA Cancer J. Clin.* **2020**, *70*, 7–30. [CrossRef] [PubMed]
6. Wekking, D.; Senevirathne, T.H.; Pearce, J.L.; Aiello, M.; Scartozzi, M.; Lambertini, M.; De Silva, P.; Solinas, C. The impact of COVID-19 on cancer patients. *Cytokine Growth Factor. Rev.* **2024**, *75*, 110–118. [CrossRef] [PubMed]
7. Allahqoli, L.; Mazidimoradi, A.; Salehiniya, H.; Alkatout, I. Impact of COVID-19 on cancer screening: A global perspective. *Curr. Opin. Support. Palliat. Care* **2022**, *16*, 102–109. [CrossRef] [PubMed]
8. Patel, N.D.; Cabrera, C.I.; Fowler, N.M.; Li, S.; Thuener, J.E.; Lavertu, P.; Teknos, T.N.; Rezaee, R.P.; Tamaki, A. Incidence and medical complications of COVID-19 in the total laryngectomy population: A population-based study. *Oral. Oncol.* **2023**, *139*, 106353. [CrossRef] [PubMed]
9. Centers for Disease Control and Prevention; National Center for Health Statistics. National Vital Statistics System, Mortality 2018–2022 on CDC WONDER Online Database, Released in 2024. Data are from the Multiple Cause of Death Files, 2018–2022, as Compiled from Data Provided by the 57 Vital Statistics Jurisdictions through the Vital Statistics Cooperative Program. Available online: http://wonder.cdc.gov/ucd-icd10-expanded.html (accessed on 4 May 2024).
10. Nocini, R.; Molteni, G.; Mattiuzzi, C.; Lippi, G. Updates on larynx cancer epidemiology. *Chin. J. Cancer Res.* **2020**, *32*, 18–25. [CrossRef] [PubMed]
11. Igissin, N.; Zatonskikh, V.; Telmanova, Z.; Tulebaev, R.; Moore, M. Laryngeal Cancer: Epidemiology, Etiology, and Prevention: A Narrative Review. *Iran. J. Public Health* **2023**, *52*, 2248–2259. [CrossRef] [PubMed]
12. Richards, M.; Anderson, M.; Carter, P.; Ebert, B.L.; Mossialos, E. The impact of the COVID-19 pandemic on cancer care. *Nat. Cancer* **2020**, *1*, 565–567. [CrossRef] [PubMed]
13. Heer, E.; Ruan, Y.; Boyne, D.J.; Jarada, T.N.; Heng, D.; Henning, J.-W.; Morris, D.M.; O'sullivan, D.E.; Cheung, W.Y.; Brenner, D.R. Impact of the COVID-19 pandemic on cancer diagnoses, stage and survival in Alberta. *CMAJ* **2023**, *195*, E804–E812. [CrossRef] [PubMed]
14. Pennisi, F.; Odelli, S.; Borlini, S.; Morani, F.; Signorelli, C.; Renzi, C. Impact of the COVID pandemic on timely cancer diagnosis across European healthcare settings: A scoping review. *Ann. Ig.* **2024**, *36*, 194–214. [CrossRef] [PubMed]
15. Mattiuzzi, C.; Lippi, G. Timeline analysis of clinical severity of COVID-19 in the general population. *Eur. J. Intern. Med.* **2023**, *110*, 97–98. [CrossRef] [PubMed]