The effect of the COVID-19 pandemic on cancer mortality due to diagnosis delay versus COVID mortality

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Abstract

Importance

In March 2020, COVID-19 made its appearance in the Netherlands after it emerged in China in late 2019. Initially, this lead to the disruption of medical care across several fields, as IC- and regular hospital beds had to be reserved for COVID-19 cases. This resulted in the delay of cancer diagnoses that can lead to adverse outcomes such as death.

Objective

By elaborating on the model of Hartmann et al. we wanted to create more insight into the effects of COVID-19 and cancer diagnosis delay on mortality.

Design, setting, and participants

We analyzed patient data of 772.517 cancer patients from 2005 to 2014 using the NCR database to establish hazard ratio's on the effect of time till first treatment, age, gender, and SES on the 5-year mortality. We used the data from 2005-2013 (n = 680.643) for analysis as train-data and the data from 2014 (n = 91.874) as test-data. The effect of time till first treatment has been used to investigate the effect of diagnosis delay on cancer 5-year mortality, whereas other variables were included for mortality risk estimates. By using open data from the IKNL we were able to calculate the expected number of cancer diagnoses per tumor type over 2020, to correct for working with a dataset from 2014. Data from the Central Bureau for Statistics (CBS) has been used to analyze the incidence and the mortality risks of COVID-19 by age and gender, which we used to calculate mortality over the test data. Results from Chavez-MacGregor et al. gave insight into the increased risk cancer patients have due to their cancer type, stage, or treatment. Lastly, we assessed all-cause mortality rates via the CBS to correct for cancer-unrelated mortality over the patient data.

Main outcomes and measures

When correcting the number of cancer cases due to working with an outdated dataset we expect 103.097 cancer cases over 2020 if COVID-19 did not occur. Of this, we calculated the 5-year mortality of 43.798 patients, which decreases by 2.96% to 42.501 due to diagnosis delay. After correcting for all-cause mortality this decreases to respectively 30.387 and 29.090, after which the mortality decrease grows to 4.27%. We expect 438 extra deaths due to COVID-19 of which 59 are allocated due to increased mortality after cancer treatment.

Conclusions and relevance

The built model can be used for the COVID-19 outbreak to assess cancer mortality versus COVID-19 mortality. It can be altered for other pandemics or sort-like outbreaks. All tumor types and stages can be assessed individually and therefore it can be used to either focus on a specific group or prioritize treatments when necessary.

Keywords

COVID-19, cancer, mortality, model, diagnosis delay

Introduction

As of the early 2022s, the world is still battling a devastating pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a virus initially identified in Wuhan, China, in December 2019 (1). The disease caused by SARS-CoV-2 is named the coronavirus disease 2019 and is colloquially known as COVID-19. Approximately two years after the World Health Organization (WHO) formally declared COVID-19 a pandemic in March 2020 (2), the global number of COVID-19 infections surpassed 450 million, and the global death toll from COVID-19 passed 6 million (3).

The initial surge of critically ill COVID-19 patients overwhelmed healthcare services across the globe. Consequently, oncological care has fallen victim to the collateral damage of COVID-19 due to the reprioritization of healthcare services in tackling the initial wave of COVID-19 (4). This disruption in oncological care—combined with alterations amid the early phases of the COVID-19 outbreak in (i) social distancing policies, (ii) health-seeking attitudes, (iii) referral practices, and (iv) temporarily halting of national cancer screening programs—contributed to a notable decline in cancer diagnoses worldwide as of March 2020 (5-10).

The gradual decrease in the demand for critical COVID-19 care towards the end of the first COVID-19 wave paved the way to recommence routine oncological care and cancer screening programs in a phased approach based on the available health workforce capacity. Accordingly, the initial decline in cancer diagnoses in the Netherlands rebounded steadily as of late April 2020. Throughout the remainder of 2020 and during 2021, the backlog of patients with cancer awaiting diagnosis has been briefly cleared, particularly when cancer screening programs for breast and colorectal cancer gradually restarted after the initial COVID-19 wave (11). Nevertheless, it seems that the backlog for screen-detected malignancies was not entirely cleared, as only May 2021 screening continued as usual (12).

In response to the initial COVID-19 outbreak, oncology professionals worldwide promptly provided recommendations to inform on cancer treatment decisions in a setting where healthcare systems are overburdened and cancer patients have a heightened risk of COVID-19-specific mortality. Nevertheless, cancer treatment should not be unduly delayed since it is well-established that delaying treatment in particular malignancies is expected to be associated with inferior outcomes. Unfortunately, due to healthcare resource constraints and patient safety concerns regarding contracting COVID-19, a delay in cancer diagnosis and management has become a reality in this unprecedented time of COVID-19. Therefore, Hartman and colleagues developed a comprehensive, web-based survival model (OncCOVID), published in October 2020, to guide cancer treatment by providing personalized quantitative estimates of overall mortality for immediate or delayed cancer treatment conditions (13).

Although the model of Hartman and colleagues was welcomed to aid treatment-decision making, it had some limitations. First, the model was rapidly established with COVID-19-related estimates during the initial COVID-19 wave, when not much was known about COVID-19 and all its effects. Secondly, the data used to estimate cancer-specific mortality and overall survival were obtained from sources across the globe with different patient populations and healthcare systems. Besides this, sex was not included in the model. Since this is a clear prognostic factor for survival in cancer and COVID-19, with men generally having a higher mortality risk than women, this can be seen as a limitation of the model (14) (15). Lastly, and most unfortunate, the model of Hartman and colleagues is not

accessible online anymore; therefore, it cannot be used anymore to assess mortality risk based on scenarios.

Given the abovementioned limitations of the model by Hartman and colleagues, we aimed to establish a model using more up-to-date data regarding COVID-19 statistics across several COVID-19 waves and one population-based source, the Netherlands Cancer Registry (NCR), to estimate mortality in patients with cancer concerning diagnosis delay during the COVID-19 pandemic and the recovery phase(16).

Methods

Introduction

We calculated the expected mortality among cancer patients over 2020 due to cancer and the effect of diagnosis delay. Simultaneously, we calculated the expected mortality among the same population due to COVID-19 and any effects on this mortality due to cancer treatment. By doing so we created an overview that can be used as a base for further studies on the subject of cancer versus COVID-19 mortality.

Cancer patient population

Data regarding the cancer patient population for this study were derived from the nationwide NCR. Information on the vital status (i.e., alive, dead, or emigration) was available in the NCR by annually linking the NCR with the Nationwide Population Registries Network which holds vital statistics of all Dutch residents. Since 1989 specially trained data managers gather data based on notifications from the pathology archive directly from patient files, including data on patient characteristics, treatment- and tumor type. We gathered data regarding diagnoses from 2005 to 2014, which was updated until January 1, 2021. Registration of comorbidities is only performed in several regions of the Netherlands and is not available on a national basis. Therefore this has not been included in the analysis. We used the group of 2005-2014 as the most recent cohorts with known 5-year mortality rates.

We selected patients from the NCR with any primary malignancy diagnosis between 2005 and 2014, yielding 1.095.343 unique tumor diagnoses. We excluded 23.798 (2,2%) diagnoses with an unknown tumor type and/or stage and 228.588 (20,9%) in whom information on the date of first-line treatment was missing. In the missing treatment cohort, we saw more diagnoses in higher tumor types than in the included cohort. Besides this, mortality rates were considerably higher. See table 1 below for a detailed description

Table 1. Missing treatment stages versus included data

Stage	Missing treatment	Included data	Ratio
0	7.996 (3,5%)	98.195 (12,7%)	0,27
1	23.536 (10,3%)	255.598 (33,1%)	0,31
2	27.951 (12,2%)	155.364 (20,1%)	0,61
3	26.758 (11,7%)	112.831 (14,6%)	0,80
4	67.401 (29,5%)	106.259 (13,8%)	2,14
M	10.686 (4,7%)	3.886 (0,5%)	9,28
NVT	64.470 (28,2%)	40.384 (5,2%)	6,15
Mortality	156.141 (68,2%)	296.366 (38,3%)	1,78
Total	228.588	772.517	n.a.

Another 59 (<0,1%) patients were excluded since the prevalence of their tumor type and/or stage was not high enough for adequate analysis. These patients were divided into 10 tumor types, of which all would be excluded in the final analysis as well due to the low event count. Lastly, we excluded 70.171

(6,4%) tumors for patients who had multiple diagnosed tumors over the included period, so that only the first diagnosed tumor would be included. The remaining 772.517 (70,5%) patients formed the basis of our analytical cohort to estimate overall survival for patients with cancer. This group was divided into two diagnostic calendar periods, namely 2005-2013 (N=680.643) and 2014 (N=91.874). A visual overview can be seen below in figure 1.

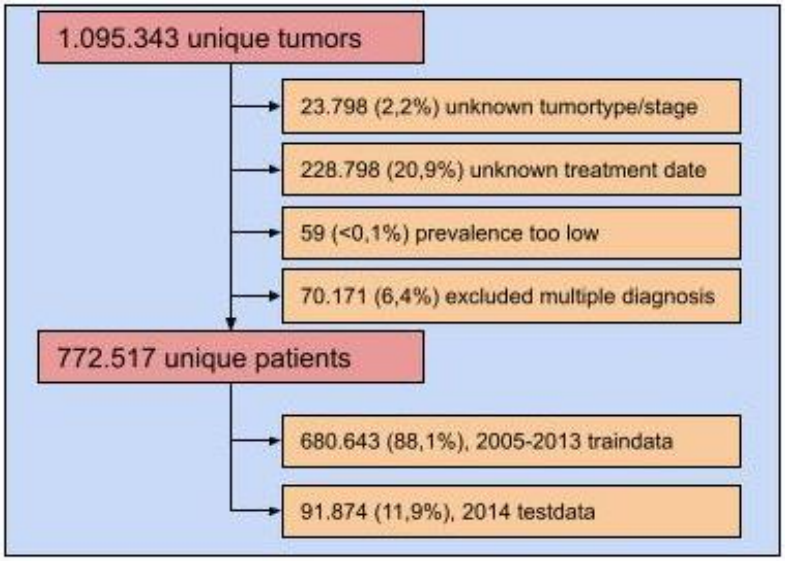

Figure 1. Exclusion criteria

The group was separated into two periods 2005 to 2013 and 2014 to use as a train- and test dataset respectively. By doing so we would not calculate hazard ratios over the same dataset as we used for analysis to prevent overfitting. The train dataset of 2005-2013 was used to analyze the effect of a delay in treatment, age, gender, and Socio-Economic Status (SES) on overall survival. The test dataset of 2014 was used to validate the developed final model. Since the treatments differ over the years this test dataset, is covered the most recent period to reflect the current daily practice the most.
Due to working with a dataset from 2014 for analysis, we had to make corrections for the number of cancer diagnoses, as this is prone to differ per year. We used a linear regression per tumor type using the number of diagnoses per year from 2005 to 2019 from the IKNL NCR database(17) to predict the expected number of cancer diagnoses for 2020 if COVID-19 would not have occurred.

COVID-19 mortality

We used data from the RIVM (Netherlands National Institute of Public Health and the Environment) (16) to analyze the mortality of covid by age group and sex, available from 1-1-2020 till 1-3-2021. This has been disaggregated between the first (27 February 2020 – 30 June 2020) and second wave (1 July 2020 – 1 March 2021) of COVID-19 to correct for treatment improvements and other possible changes influencing COVID-19 mortality. Due to a limitation of available testing capacity in the first wave, estimates of death tolls and covid infections had to be made. Death tolls have been adjusted for probable deaths using data from the Statistics Netherlands (CBS) (18). We adjusted the estimated amount of people who contracted covid using the ratios of hospital admissions by age group and sex using the data from the RIVM(16). We assumed that patients who were admitted to the hospital with covid-like

symptoms were tested on equal conditions during the first and second wave and that the burden of disease was equally leading to an equal rate of patient admissions. By doing so a more accurate overview of the covid situation has been estimated. These calculations lowered the mortality rate from the known CBS (16) data of 21,46% to 1.22% for males and from 10,69% to 1,07% for females. With mortality rates in the second wave of 1,10% and 0,83% for males and females respectively, this substantiated our calculations to be better fitting, keeping potential treatment improvements in mind.

Diagnosis delay

Unfortunately, no information on patient level was available for treatment delay. However, data was available about the number of cancer diagnoses per tumor type and stage, as defined by the IKNL by tumor group level(19), over 2019 and 2020, which gave insight into possible diagnoses delays. By comparing the cumulative amount of diagnoses per week across 2019 and 2020 we estimated a delay for patients. Time to diagnosis delay was calculated using the cumulative number of diagnoses for 2019 and 2020 separately, where we analyzed the difference in time before equal amounts of diagnoses were reached. For this, we assumed there was no significant in- or decrease of cancer cases between 2019 and 2020 except due to any influence of COVID-19, given they are contiguous years.

Statistical analyses

For final analysis, we built a model in Microsoft Excel 2016 (20). We used the variables time till first treatment, age (ranging 18-106), SES (ranging from 0-10), sex (male and female), treatment type (chemo-, radio-, Bracy-, hormonal-, targeted- and unknown type of therapy) and incidence week. The type of treatment, tumor stage and tumor type have been used to assess any effects on covid mortality, as researched by Chavez-MacGregor et al. (21). According to their results, patients have an increased mortality risk up to 3 months after their treatment for several treatments. As revealed in their research, there is a hazard rate of 1.74 ($p < 0.001$) in the first 3 months after treatment for dying due to COVID-19. Metastatic tumors have proven to lead to increased risks as well ($HR = 2.36$, $p < 0.001$) besides hematologic malignant tumors ($HR = 1.72$, $p < 0.001$). Outcomes of the analysis were the mortality rates for both cancer and COVID-19, broken down by tumor type and -stage.

To prevent the model from becoming too complex we, unfortunately, had to calculate the incidence and mortality risk due to COVID-19 from the week of diagnosis instead of the calculated treatment date.

We used data from the CBS(22) on regular mortality rates to investigate the relative burden of the effects of covid and diagnosis delay on total mortality. Since the NCR database does not include the cause of death, this gave us better insight into the percentual alterations due to both COVID-19 and diagnoses delays.

For the model, we only analyzed tumor types and stages which had an event rate of at least 40 in the source data (2005 to 2013) using the one in ten rule.

The data of 2005 to 2013 was used to analyze the hazard ratio of diagnoses delays on overall survival, categorized by stage and cancer type, as defined by the ICD-0-3 categorization. All HRs used were either significant ($p < 0.05$) or altered as being 1 when there was no significant effect detected.

Statistical analyses were conducted using Stata statistical software: Release 17 (23) using a cox regression with the Breslow method for ties.

Results

With the built model, we were able to analyze the effects of COVID-19 and diagnosis delays. It is composed in such a way that any alterations required for further analysis can easily be incorporated. It has been separated per tumor type and stage resulting in an extensive overview. With the current model, we have patient data for 300 tumor types and stages, of which 202 could be included due to the set limit of >40 events per type and stage. We were able to analyze 90.188 (98,2%) out of 91.874 cases, which after adjustment for differences in cancer diagnostics per year resulted in 103.097 expected cases over 2020.

Patient characteristics

In table 2 below a detailed overview of the included patient cohort can be seen. For the overview we have mentioned the cancer types per main group instead of subgroup, since listing all used cancer types would not be feasible.

Table 2. Patient characteristics

	2005-2013 train cohort		**2014 test cohort**	
Included patients	680.644		91.874	
Age	65,0	St.dev 13,8	65,6	st. dev 13,5
Male	320.886	47,1%	44.070	48,0%
Female	359.757	52,9%	47.804	52,0%
Mortality	238.861	35,1%	31.445	34,2%
Head and neck cancer	21.058	3,1%	2.612	2,8%
Digestive tract	125.650	18,5%	18.384	20,0%
Respiratory tract	57.789	8,5%	8.170	8,9%
Skin	139.134	20,4%	19.377	21,1%
Bone, articular cartilage, and soft tissues	132.315	19,4%	16.247	17,7%
Breast	34.085	5,0%	4.009	4,4%
Female genital organs	124.325	18,3%	15.324	16,7%
Male genital organs	30.106	4,4%	5.686	6,2%
Urinary tract	16.501	2,4%	2.101	2,3%

Validation

We have calculated the expected cancer mortality for the cohort of 2014 from the train data gathered over 2005 to 2013. According to the outcomes of the train-data, we calculate 32.926 deaths, versus 31.445 actual deaths, which is 4,7% higher. These outcomes have not been corrected for increases in diagnoses over the years and therefore only include analysis over actual cases.

Covid mortality

We calculated the expected infection rate over patients per tumor type and stage. On average patients have a 12,1% chance of COVID-19 infection, of which 2,6% is during the increased-risk period of 3 months after treatment. Patients experience an average 3,2% mortality rate calculated on the base of their age and sex, with an additional 2,6% mortality rate in the 3 months after treatment. However, this varies per patient as it also depends on tumor type, stage, and treatment (21). In total, we expect 438 COVID-19-related deaths, of which 59 (13,4%) are related to increased mortality after cancer treatment.

Cancer mortality

According to our calculations, we expect a 5-year mortality of 42.501 patients (41,2% of the corrected population) due to cancer and all-cause mortality, which is a decrease of 1297 if no delays would have occurred. Of the total 43.798 expected deaths, this translates to a decrease of 3,0%. The weighted average hazard ratio for time till first treatment is 0,998. This corresponds with the decrease in deaths, as mortality decreases with delays, but the effect varies per tumor type and stage besides varying lengths of diagnosis delays. When correcting for all-cause mortality, which accounts for 13.411 deaths (36,7% of total expected mortality), the total mortality remains at 29.090 deaths, resulting in the percentual decreased mortality due to diagnosis delay increasing to 4,2%. We see an initial response of higher mortality in the first 15 days after diagnosis, as can be seen in figure 2 below. Patients with an initial treatment after 150 days have not been included in the figure (n=7711, 1,1%).

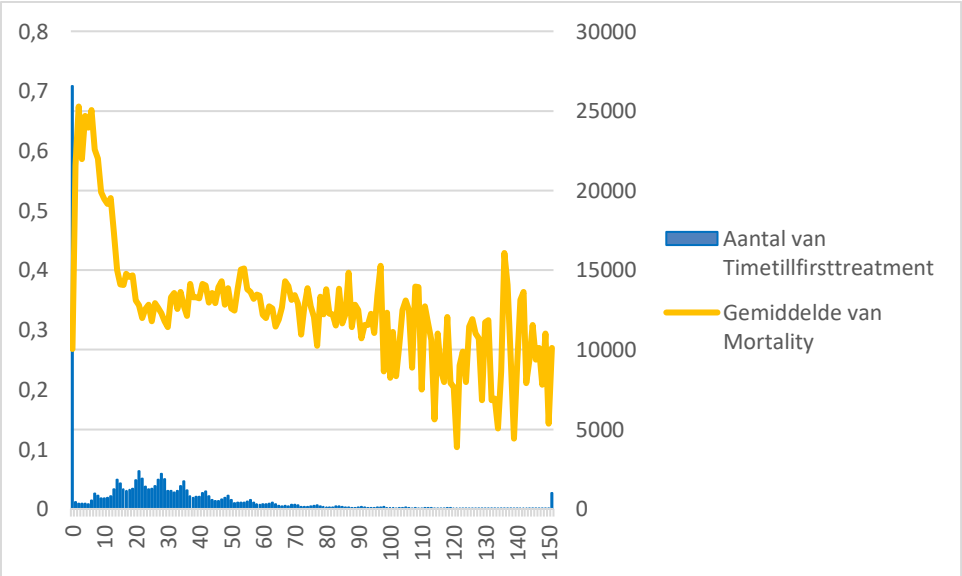

Figure 2. Average mortality rate by time till first treatment (in days).

Discussion

In total, we expect a net decrease of 859 deaths on 5-year mortality over the cohort of patients due to either COVID-19 (+438) or diagnosis delay (-1297). A possible explanation for the decrease in cancer mortality might be that patients with high-risk profiles get treated early, resulting in the analysis seeing early treatment as negative for survival. This can be seen in figure 2, where the average mortality slowly declines over time. However, we could not investigate if our assumption is correct or if there might be another explanation for this outcome.

Strengths and limitations

This study has several limitations, among several assumptions that had to be made due to it being a prospective modeling study. No data regarding treatment delays or alterations were available on patient level, which limited us to determining the delay from the cumulative number of diagnoses. Besides this, estimates were made on the number of diagnoses and deaths during the first covid wave in 2020. In addition, the regular mortality rates have been calculated by age and sex only and might not be an adequate representation of reality. Cancer patients are prone to having a more complicated medical file making a comparison to the regular population difficult. However, by including it in the analysis we can give a better overview of the percentual change. Lastly, for proper analysis, we worked with no significant in- or decrease between 2019 and 2020, although these do occur. As the years are consecutive, these differences are seen as minor and therefore not significant.

Comorbidities could not be included due to the low availability in the NCR. From several treatments, it was known that they have effects on covid-survival due to Chavez-McGregor et al. (21), although this is still with initial data regarding COVID-19. Besides this, the included period only includes the initial strain of COVID-19 and not Alfa, Delta, and Omikron, which have all been dominant in the Netherlands since. With different clinical pictures, this might lead to different outcomes when assessing later waves of COVID-19. However, the model can easily be altered to fit these situations.

With the model, we have created an opportunity to assess mortality within patient groups per tumor type and stage, which was not fully available in the model of Hartmann and colleagues. We deem it unfeasible to assess mortality rates for individual patients, as numerous patient characteristics influencing outcomes make predictions unreliable. By looking at a larger population instead of a single patient, variations are averaged and more certainty can be provided.

Conclusion

We have developed a model which can be used to assess the effects of covid mortality and effects of diagnosis delay for cancer patients. The model differs from Hartman et al. (13) as it is not usable on the patient level, but offers more flexibility in the number of available tumor types. Besides this, data was used from the Netherlands in all situations where possible, with the outcomes of Chavez-MacGregor et al. (21) being the sole exception. The model can be used as a baseline for coming outbreaks or pandemics and suchlike crises, due to its flexibility in variables. Modifications can be made according to available data and factors which are or are not present. It can be used both as a factor to estimate outcomes or to establish which patient groups should be treated first. Valuable information such as high-risk patient groups for delay or high mortality due to infectious diseases or cancer can be extracted in

its current state while it can be expanded to focus solely on certain patient groups if desired. The model can be used to assist in decision-making processes and cost-benefit analysis on all levels of policy-making except patient-level, making it valuable for hospitals, national health agencies, and research facilities.

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