The Association of Schools of Public Health in the European Region

Understanding the concept of excess mortality; Analysis of direct and indirect effects of COVID-19 on cancer care services in the United Kingdom

[Master Thesis-Executive Summary]

By
Pallavi Ch

Supervisors: Prof. Ralf Reintjes (HAW-Hamburg)
Prof. John Middleton (ASPHER, Brussels)

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List of Abbreviations

AHMAC	Australian Health Minister’s Advisory Council
APSDE	Asian Pacific Society for Digestive Endoscopy
A&E	Accident & Emergency
COVID-19	Coronavirus disease 2019
CT Scan	Computed Tomography scan
ECDC	European Center for Disease Prevention and Control
EM	Excess mortality
EU&EEA	European Society of Gastrointestinal Endoscopy
EuroMOMO	European Mortality monitoring project
FIT	Faecal Immunochemical Test
GP	General Practitioner
LYG	Life year gained
MRI	Magnetic resonance imaging
NCD	Non-communicable disease
NHS	National Health Service
NIH	National Institute of Health
NICE	National Institute for Health and Care Excellence
OECD	Organization for economic co-operation and development
ONS	Office for National Statistics
QALY’s	Quality Adjusted Life Years
RT-PCR	Reverse transcription-polymerase chain reaction
SARS-CoV-2	severe acute respiratory syndrome virus 2
SACT	systematic anti-cancer therapy
UK	United Kingdom
USA	United States of America
USG	Ultrasonography
YLL	years of life lost
WHO	World Health Organization
111	Free to call single non-emergency number medical helpline in England

1 Abstract

Background including aim: The reported number of COVID-19 deaths is likely to be an under representation of overall deaths attributed to the pandemic even when deaths mentioning COVID-19 in any section of the death certificate are included. This reflects the impact of COVID-19 on the trajectory of other illnesses, disruption to health and care services, avoidant help seeking behaviour and extended use of non-pharmacological measures. The impact of these pandemic policies was significant among those who are suffering from underlying comorbidities, particularly cancer. In this regard, the concept of excess deaths caused due to COVID-19 can be considered a better measure to estimate the effect of the pandemic which includes both direct and indirect deaths. The purpose of this study is to conduct a narrative review of published literature to understand the direct and indirect effects of the pandemic and related policies on the cancer care pathway and to approximate the number of excess deaths due to COVID-19 in cancer patients in the UK.

Methods: A comprehensive literature search was conducted using online databases and relevant articles were found and included. Reports from the UK's government official websites, WHO, IHME, and ECDC were reviewed and included. UK's public health and cancer registry websites were searched for data on cancer care pathways, routes to cancer diagnosis, and service impacts during COVID-19.

Results: Literature suggests that there are both direct and indirect effects of the pandemic on oncology services. Direct effects: during the first pandemic wave, the all-cause mortality and excess cancer deaths were high in England at 198,794 and 45,272 respectively followed by Scotland at 21,169/102; Wales at 11,852/61 and Northern Ireland at 5,353/75. Indirect effects: delayed cancer diagnosis would cause 3,291 to 3,621 avoidable cancer deaths and the years of life lost (YLL) among cancer patients were estimated to be between 56,204 to 63,229. Delays in the surgical treatment of incident solid tumours by three months and six months would result in 4,755 and 10,760 excess deaths respectively over the 12 months.

Conclusion: Under-reporting of COVID-19 deaths has resulted in an incomplete understanding of the true burden of the pandemic. Health policy narratives during public health emergencies are effective provided there is reliable reporting and timely availability of mortality data. Thereby many excess avoidable deaths might be prevented. Also, excess mortality can be used as a measure to understand the indirect effects of the pandemic on people with underlying conditions. Further, significant research regarding the use of excess deaths as a measure for assessing the indirect effects of the pandemic is crucial.

Keywords: COVID-19, excess deaths, pandemic policies, UK

2 Background

The pandemic started in China in late 2019 due to SARS-CoV-19 which is a zoonotic virus. The virus has been evolving rapidly to date and has become a major global health concern. On March 11, 2020, World Health Organisation (WHO) declared the COVID-19 pandemic (1). The mean incubation period of SARS CoV-2 is 5- 6 days, though it can range from 1-14 days depending on the variant and the rate of reproduction of the virus which is detailed in Table 2 (2).

Table 1: The epidemiological characteristics of SARS CoV-2 and its variants

Virus and variants	**Incubation period**	**R-value (Basic reproduction number R_0)**	**Infectiousness (in terms of hospitalization and ICU admission)**
SARS-CoV-2	5-6 days, can be up to 14 days [9] [10]	2 to 2.5 [11]	Higher than influenza [12] [13]
Alpha	Approx. 3 days [14]	Higher than other variants	Higher hospital and ICU admission rates particularly among the young age group
Beta	N/A*	1.50 times as transmissible as previous variants [15]	Causes more severe disease (based on initial studies)
Gamma	N/A*	Mixed evidence / higher frequency	Causes severe course of disease (based on initial studies)
Delta	Approx. 4 days [22]	5.10 (3.04 to 7.17) [16]	Double than Alpha [17]
Omicron	Shorter than Delta [18]	9.5 (5.5 to 24) [19]	Lower than Delta (in hospitalizations) [8]

*This information is not available to ascertain these parameters.

The virus is transmitted from person to person through respiratory droplets by close contact (15) by short-range aerosol or short-range airborne transmission (16) or Long-range aerosol or long-range airborne transmission (17). The indirect mode of transmission occurs by contacting the surfaces or objects contaminated by the infected individual (fomites) followed by touching the mucous membrane. The virus can stay on surfaces for a long time. However, respiratory droplet transmission is the predominant mode of transmission of the SARS-CoV-2 virus compared to fomite transmission (17). The clinical presentation of COVID-19 ranges from asymptomatic illness to severe pneumonia and death (2).

The most common symptoms of COVID-19 include fever, cough, fatigue, and loss of taste or smell and the uncommon symptoms are sore throat, myalgia, headache, nausea or vomiting, diarrhoea, rash on skin and congestion of eyes and nose. The symptoms of severe COVID-19 are shortness of breath, chest pain, loss of speech or moment or altered sensorium (18) (19). Based on the severity level of clinical presentation, COVID-19 patients can be classified into mild, moderate, severe, and critical diseases (20) (21) (Table 3). Symptom clusters among older people and those with underlying comorbidities include the absence of fever, altered sensorium, fatigue, diarrhoea, and neurological deficits (22).

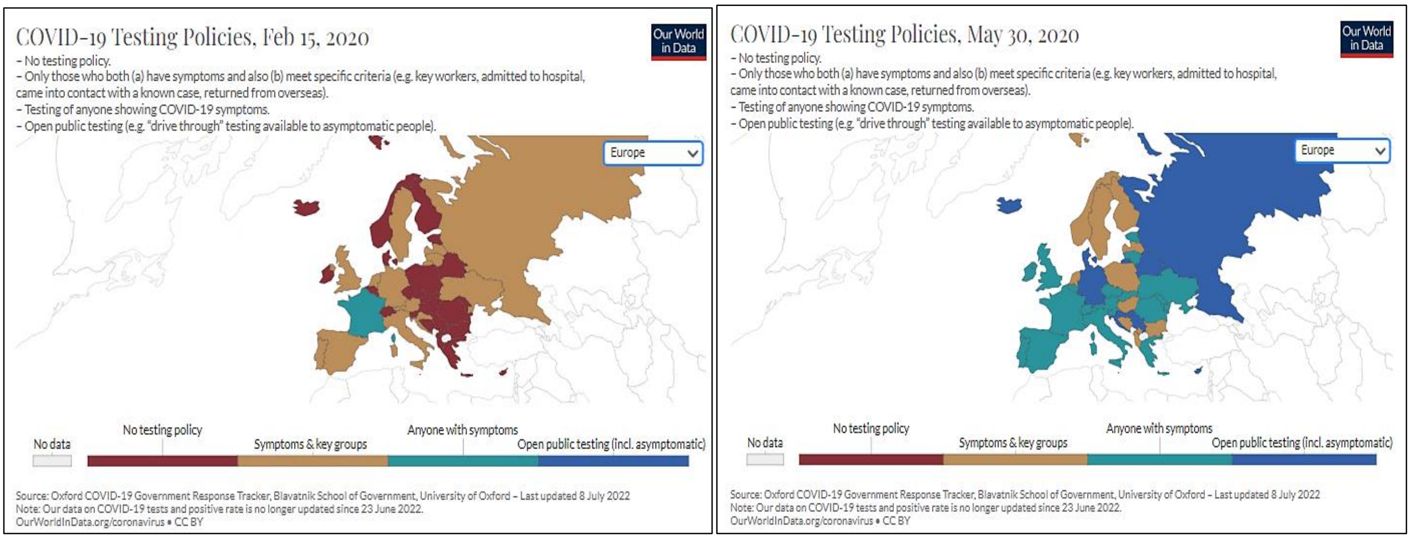
Table 2: Clinical presentation of COVID-19

Severity level	Symptoms
Mild	Symptomatic patients who meet the WHO criteria of COVID-19 case definition and have no signs of pneumonia or hypoxia
Moderate	Sings of pneumonia- Fever, cough, difficulty in breathing and tachypnoea SpO_2- ≥ 90% on room air
Severe	Severe pneumonia with SpO_2 <90% on room air
Critical	Acute respiratory distress syndrome (ARDS), Sepsis, Septic shock

Source: Adapted from WHO clinical management of COVID-19, Interim guidance, 27 May 2020 (22)

COVID-19 is diagnosed through laboratory PCR tests using nasal or nasopharyngeal or oropharyngeal swabs (23). Although the RT-PCR technique is the gold standard procedure, limitations such as lack of consistency, time constraints involving labour and short supply of the material to perform the test caused a delay in reporting. These were the main pitfalls in the process (24). Although the testing policy is one of the key strategies to control the speed of transmission, there was a wide variation between the countries' testing policies from the beginning of the pandemic (25) (26) (Figure 1).

Figure 1: Variation in testing policy in Europe between the end of February and May 2020



Source: Taken from Our World in Data, COVID-19 Testing Policies (26)

Radiological imaging has its own importance in the diagnosis of both suspected and possible COVID-19 patients particularly when the laboratory findings (RT-PCR test) are inconclusive. The predominant radiological features of COVID-19 are ground glass opacities in bilateral peripheral lung fields and consolidation in computed tomography (CT) (27) (28). Because of the complex and inconsistent nature of COVID-19, there is no definitive treatment and patients are treated symptomatically (29). The National Institute of Health (NIH) established guidelines for the management of patients according to the severity of illness and they are regularly updated (30) (31). The following drugs are used alone and/or in combination based on the severity of illness - Antiviral drugs, anti-inflammatory drugs (Dexamethasone), immunomodulatory drugs (Tocilizumab, Baricitinib, Sarilumab) and prophylactic or therapeutic dose of anticoagulants (Heparin) (32).

The virus can affect any age group. However, the risk of severe illness and mortality due to COVID-19 increases with age (33). Studies from the UK (34), USA (35) (36) and China (37) (38) show that the median age of hospitalization with COVID-19 symptoms ranges from 50 years to 73 years with predominance in males. Underlying comorbid conditions such as malignancy, diabetes, hypertension, neurological conditions, chronic respiratory diseases, cardiac conditions, and kidney diseases also contribute to higher morbidity and mortality (2) (39). According to joint information from WHO and United Nations Development Program (UNDP), and the Centre for Disease Control (CDC), obesity, smoking, alcohol, air pollution, and physical inactivity were identified as the risk factors for COVID-19 (40) (41).

Initial studies proved that COVID-19 is preventable through non-pharmacological interventions such as maintaining social distancing, wearing a face mask, hand hygiene, home or institutional quarantine, travel restrictions, and schools closure (42) (43) (44). Further, to bring down the reproduction rate of the virus below 1, countries followed mitigation or containment (or suppression) or elimination (or aggressive suppression) strategy or herd immunity strategy (45). Only Sweden and a few counties in Brazil followed the herd immunity strategy during the initial weeks of the pandemic (46) (47). Most countries for ex. USA, France and Germany implemented the mitigation strategy. Whereas China and New Zealand have controlled the pandemic effectively by adopting elimination strategy. The purpose of the elimination strategy is to maintain the incidence at zero or very low level. Few other countries such as Australia, Singapore, South Korea, and Thailand have implemented containment strategy (45) (48).

Simultaneously, vaccines were developed to protect against the risk of severe illness and death from COVID-19 and its variants. Vaccine rollout began in early December 2020 (49). Individuals who are at high risk of infection such as the elderly age group and health care workers were vaccinated at first, followed by adults and children (50). Globally, over 8.5 billion (8,687,201,202) vaccine doses were administered by the end of December 2021 (51). Although, WHO set up vaccine priorities and global targets, supply constraints and vaccine hesitancy were the main challenges, particularly in middle - and low-income countries (52).

3 Introduction

By the end of March 2022, the global level incidence of confirmed COVID-19 cases reported by WHO is more than 4.5 billion (51). The official statistics on the reported number of COVID-19 deaths are likely an underrepresentation of overall deaths attributed to the pandemic (53). At the beginning of the pandemic, many COVID-19 deaths were not documented due to the lack of COVID-19 death definition and confirmed test reports. Also, COVID-19 deaths in care homes were missed in many countries and were not included in all deaths attributed to the pandemic (54). Further, the underlying cause of death of COVID-19 was misinterpreted, particularly in the death of a person who had comorbidities, the cause of death was wrongly assigned (55).

In many countries particularly, low-and middle-income countries there is no well-established pandemic surveillance system which affected the quantification of the mortality impact of the pandemic. Even in those countries with a strong surveillance system, the scale of the pandemic caused challenges to the timeliness of death registrations and the comprehensiveness of quality checks (56). However, these mortality statistics do not provide information on indirect deaths caused during the pandemic due to pandemic policies such as lockdowns, stay-at-home orders, and social distancing measures.

3.1 Disruption of Care pathways

During the pandemic, many healthcare services that were needed were either postponed or delayed because of concerns about the spread of the pandemic (57). Social distancing measures, lockdown and stay-home orders further impacted access to healthcare services other than COVID-19. A survey by the WHO on assessing the effect of the pandemic on healthcare services for non-communicable diseases (NCDs) comprising 155 countries during May 2020, revealed that access to major and essential healthcare services was hampered significantly (58). Social distancing also affected those people with mental and physical disabilities, the old age group and residents in care facilities who need continuous care and support services (59). Moreover, people were hesitant to attend the hospitals due to fear of contracting the virus (60).

However, data explaining the association between disrupted health care and indirect deaths due to the pandemic is lacking. It could be possible that these deaths might have occurred due to the disruption in health care together with the change in attitudes towards health care service that might have contributed to the indirect deaths during the pandemic (61). Unlike the direct causes of death, indirect causes of death statistics are not available immediately.

On the other hand, due to the pandemic mitigation measures, there was a decline in deaths due to road traffic accidents. Studies from Europe (62) and India (63) showed that the number of traffic accident fatalities reduced significantly during the first wave of the pandemic. Furthermore, due to social distancing measures, a decrease in mortality due to respiratory diseases (other than COVID-19) such as influenza and asthma (64) (65) was observed. Given the variation in the surveillance capacity and reporting COVID-19 deaths among countries, it is challenging to analyse the overall mortality impact attributed to both direct and indirect causes of the pandemic. Therefore, excess mortality (EM) is used frequently to compare coronavirus deaths between the countries despite the existing variations (66).

3.2 Epidemiology of COVID-19 in the UK

The UK is one of the countries in the world most affected by the COVID-19 pandemic. On 5th March 2020, the UK officially reported its first COVID-19 death (though it happened on 2nd March in a care home elderly woman aged 70 years with underlying comorbidities) (67). By mid-April 2020, the 7-day average of daily reported COVID-19 deaths in the UK reached 1351.58 deaths. The death toll was high in England at 1185.35 compared to its counterparts (Wales 58.5; Scotland 93.01; Northern Ireland 14.73 (68). Nearly two weeks after the first COVID-19 death, a sharp rise in excess all-cause mortality was observed (69). The registered number of deaths as well as the excess all-cause mortality were high in England during this period, ever since 2015/16 (69). While acknowledging the care services towards emerging COVID-19, the non-communicable disease burden such as cancer, cardiovascular disease and mental health had risen which reflects the indirect effects of the pandemic (70) (71).

3.3 Cancer and COVID-19 in the UK:

Cancer is the most common cause of death in the UK (72). Cancer patients are at more risk of COVID-19 infection, hospitalization, severe clinical illness and death compared to the general population (73). Several factors such as a cancer patient’s immunocompromised status, cytotoxic treatments, and pre-existing comorbidities may have contributed to their increased risk of COVID-19 infection (74). Also, the probability of severe illness and death is strongly associated with a history of recent chemotherapy and the intensity level of clinical therapy at the time of admission (75) (73).

Studies on the characteristics of COVID-19 cancer patients revealed that there is an association between the severity of COVID-19 and the type and stage of cancer (76) (77). Due to the COVID-19 pandemic, healthcare systems were overwhelmed to the extent that the regular care services including cancer had to be reorganized alongside combating COVID-19. New regulations were reinstated by cancer care organizations to modify cancer care services including screening, diagnosis, referrals, radiotherapy, chemotherapy, and surgical treatment at national and international levels. Cancer Core Europe has endorsed guidelines for oncology practice to manage systematic anticancer care treatment. However, England's NHS Guidance was the most widely practised (78).

Although cancer care services were prioritized throughout the pandemic, the number of people utilizing these services was reduced. Owing to the fact that there were pre-existing (before the pandemic) barriers throughout Europe including the UK to perform breast, cervical and colorectal screening tests such as a lack of trained personnel, materials, financial resources, and technical and managerial operations (79). The impact of these pre-existing capacity limits might have been exacerbated during the pandemic because of staff sickness, physical distancing requirements reducing the number of people that can be treated at one time and lack of suitable alternative settings to keep the number of patients treated at pre-pandemic level (80). As a result, the UK experienced excess deaths directly attributable to COVID-19 and excess cancer deaths caused directly and indirectly during the first wave of the pandemic.

This review aims to 1) explore the concept of excess mortality and assess the excess mortality during the pandemic and 2) analyse both the direct and indirect effects of COVID-19 on cancer care services in the United Kingdom.

4 COVID-19 death definition and reporting by WHO

To identify the number of deaths related to COVID-19 across nations in April 2020, WHO introduced guidelines for the documentation of COVID-19 deaths and established clear definitions for covid fatalities as follows (81) (82). "*A death due to COVID-19 is defined for surveillance purposes as a death resulting from a clinically compatible illness, in a probable or confirmed COVID-19 case, unless there is a clear alternative cause of death that cannot be related to COVID disease (e.g., trauma). There should be no period of complete recovery from COVID-19 between illness and death. A death due to COVID-19 may not be attributed to another disease (e.g., cancer) and should be counted independently of pre-existing conditions that are suspected of triggering a severe course of COVID-19.*"

4.1 How countries have defined COVID-19 death

During the early phase of the pandemic, universal guidelines were not available and hence countries were driven by their own standards to define COVID-19 deaths. For instance, Belgium adapted the most all-encompassing definition of coronavirus death by including both laboratory-confirmed and possible cases (meeting the clinical criteria of COVID-19) at care homes. Whereas, Russia was entirely dependent on autopsy reports to confirm the cause of death (83). There is variation in concluding whether it was a COVID-19 death within each country, as well as between the countries. Italy adapted strategies for reporting COVID-19 fatalities which are different across all regions of the country. Some of the regional authorities excluded deaths at home and in residential care homes. This was further influenced by the country's testing capacity (84). Additionally, COVID-19 death certification rules also differed between the countries (85).

Table 4 shows the adapted definition of COVID-19 death by individual countries. A positive laboratory PCR test and clinical diagnosis (probable or confirmed) are the two methods the nations have relied upon in defining a death due to COVID-19. However, some countries followed both clinical diagnosis and a positive laboratory test to confirm COVID-19 death (86). Consequently, the reported number of deaths is more in countries that report the cause of death based on clinical diagnosis than those that rely on the laboratory confirmation test. Although the RT-PCR technique is the gold standard procedure, limitations such as lack of consistency due to time constraints, short supply of labour and testing kits delayed the test reporting (24).

Table 3: COVID-19 death definition followed by the countries

COVID-19 death based on Clinical diagnosis (probable and confirmed)	Australia, Belgium, Bulgaria, Canada, Croatia, Cyprus, Estonia, France, Germany, Greece, Ireland, Israel, Latvia, Lithuania, Malta, New Zealand, Poland, Portugal, Serbia, Romania, USA
COVID-19 death based on the laboratory confirmation test	Austria, Bosnia and Herzegovina, Cyprus, Czech Republic (87), Denmark (88), Finland (89), Greece, Hungary, Iceland, Italy, Netherlands, Norway, Serbia, Slovenia, Spain, Romania, Sweden, Switzerland, United Kingdom
COVID-19 death based on both clinical diagnosis and laboratory test	Cyprus, Greece, Romania, Serbia

Source: Adapted from Karanikolas et al. How comparable is COVID-19 mortality across countries (86)

4.2 Concept of excess mortality

Mortality data is a widely used source of information and an important indicator of a population´s health. Whereas, the estimation of excess deaths during an epidemic outbreak determines the virulence of the disease and the overall disease burden in a population (90). Hence, epidemiologists consider EM as a better mortality indicator during the emergency situation of an epidemic/pandemic. Excess mortality (EM) is the difference between the number of observed deaths and expected deaths (which otherwise would not have happened if the outbreak has not occurred). The expected number of deaths is assumed based on the historical data approach (91).

A better understanding of the EM helps to track the progression of the pandemic and to execute public health strategies (92). Additionally, these statistics are useful to see how comparable it is with previous years and to predict the changes over time (93). In the absence of prevalence data, EM serves as an alternate source of information on the disease spread (90). The concept has been well-established by experts in the field of Epidemiology and Demography (55). The concept of EM for the first time was used by the Swiss federal authorities during the 1890 influenza pandemic in Switzerland. They evaluated the difference between the mortality during the pandemic year and the adjacent years (94).

In the past 140 years, Europe had suffered several Influenza pandemics (94). The pandemic in 1918 was the most devastating of all in the 20th century and accounted for many deaths in Europe. A study by Ansart et al comparing the impact of the 1918 Influenza pandemic among 14 European countries determined that the EM impact was 3.5 times higher compared to the years from 1906 to 1922 (95). Analysis of the EM considering the seasonal mortality fluctuations in Europe showed the effect of the pandemic in a new light (95). Because the seasonal mortality influences the overall mortality in that year. Other than influenza, factors associated with an increase in mortality such as high-risk age group, cold temperature, indoor environment, clothing, and heat waves were studied elsewhere (96)

(97). However, factors such as virus pathogenesis, diagnosis, interaction with underlying comorbidities, and assigning code to the cause of death have influenced the flu mortality statistics (55).

4.3 How to measure excess mortality?

To obtain EM, the total number of deaths from all causes observed during crisis conditions is considered. The total number of deaths from all causes includes direct deaths attributed to the crisis condition and indirect deaths due to overburdened health systems and social disruption. Expected deaths are derived using historic data from the previous non-pandemic years (92) (98).

"Excess deaths = Reported deaths - Expected deaths" (99)

Reported death data is available from the official statistics maintained by the individual organizations. However, to derive expected deaths, there is no universal consensus. The difference between these two parameters is compared with the preceding year's average (historical average) and any variation is counted as an excess that would not have happened if the pandemic had not occurred. Although it is the common method used to derive excess deaths, caution should be employed while interpreting. Because mortality data from the preceding years might have unusually high mortality due to extremes of temperature or seasonal outbreaks in that particular year (55).

4.4 What is the baseline to be considered?

When estimating the expected deaths, what is the baseline to be considered is a major concern. The Serfling method was the conventional method used to assess excess winter mortality. This model captures annual cyclical variation. Using this method, a standard expected seasonal mortality curve was established thereby excess deaths were measured in comparison with this curve (100). Any deviation from the baseline curve represents EM (101). During the 2009/2010 swine flu pandemic, the European mortality monitoring project (EuroMOMO) applied this Serfling method to estimate cyclic variation in influenza mortality. This was because Influenza epidemics are highly seasonal with peaks occurring in the winter months (55). The proportion of excess deaths derived depends on the type of model and the parameters included or excluded in the baseline such as mortality adjusted for extremes of temperature, deaths from circulatory diseases, and periodic influenza outbreaks. Hence, estimating the baseline is vital.

4.5 Excess mortality due to covid-19

COVID-19 excess mortality is attributed to both the total number of deaths due to COVID-19 together with the number of deaths that occurred as an indirect consequence of movement restrictions, suspension of both essential and non-essential services and disruption of access to major health facilities (102). Nevertheless, excess deaths would also include a reduced number of deaths from road traffic accidents, air pollution and other infectious diseases due to the effect of preventative measures such as social distancing, wearing a face mask, and the stay-at-home order (103) (104) (105). This reduced number of deaths from other causes was reflected as negative excess or deficit deaths (92).

In COVID-19 measuring excess deaths at global, regional, and national levels is challenging. Because the provision of the data from several countries to the systematic mortality surveillance is missing given the heterogeneity in the COVID-19 testing policies and capacity, and timeliness in reporting COVID-19 deaths. The lack of all-cause mortality data is another limitation to estimate excess deaths. Additionally, there is a variation in the death reporting systems across countries. Also, only a few countries (high-income countries) provide routine high-quality data (92).

A lot of research has emerged on estimating COVID-19 impact through EM at a national level and its comparison at an international level. However, the methodology used to estimate the baseline period and the reference range of the historical data to project excess deaths vary from study to study (98) (106) (107) (108). (Appendix I). None of the studies accounted for population age structure (which is inconsistent), mortality risk factors and other health explanatory variables (109) in the reference period. Therefore, caution is needed while interpreting the excess deaths at a multinational level.

WHO's recent estimate of EM at the global level for the years 2020 and 2021 was nearly 14.9 million. The proportion of excess COVID-19 deaths accounted for by low, middle, and high-income countries was 4%, 81%, and 15% respectively. Overall, more than 80% of the EM was attributed to the Americas, Europe, and South-East Asia regions of WHO. The estimates also provided age and sex-disaggregated covid excess deaths data. According to the data, globally there were more deaths among men compared to women at 57% and 43% respectively and the old age group suffered a greater number of deaths. However, depending on the population size the absolute number of mortality statistics varies. Therefore, an assessment of the number of excess deaths per 100,000 population provides a better understanding rather than counting the reported number of covid deaths (110).

4.6 Is excess mortality a better indicator of overall COVID-related mortality?

Excess mortality is mortality beyond the normal range. The purpose of assessing EM due to the pandemic is

- due to the lack of sufficient testing capacity, many COVID-19 deaths were not reported or misinterpreted. Measuring EM outstrips these limitations (111).
- to understand the overall effect of COVID-19 on fatality, as EM encompasses not only deaths due to COVID-19 (direct deaths) but deaths from all causes such as deaths due to delays in attaining routine and emergency health care services (indirect deaths) (111). For example, cancer screening services and physician urgent referrals for suspected cancer were interrupted in many countries which increases the mortality risk. This might impact excess deaths directly or indirectly attributed to COVID-19 (112).
- to interpret the differences in defining and reporting COVID-19 deaths by countries that did not reflect the total COVID-19 (including excess) deaths from all causes. For instance, France reported COVID-19 deaths all-inclusive from the community whereas Italy reported only deaths from hospitals. In the UK, the national-level mortality statistics refer to the information on the death certificate (which is usually filled out by medical practitioners). Whereas Germany, Austria, and Portugal reported every death with confirmed SARS-CoV-2 infection as a COVID-19 death (113)
- tracking EM over time and across countries, particularly when disaggregated by age and gender helps to evaluate the causes that might have contributed to excess mortality among particular age group and gender (114). Also, tracking EM helps to assess the positive and negative contributions of health policies intended to mitigate the pandemic.
- Finally, knowledge of EM aids in analysing not only the mortality burden but also the social and economic consequences of the pandemic due to lockdown restrictions (115).

Hence, the above reasons claim that EM is a better metric to assess both the direct and indirect effects of the pandemic.

5 Methods

An extensive literature search was done to develop this narrative review using the search terms such as ‘COVID-19’, ‘SARS-CoV-2’, ‘Mortality’, ‘United Kingdom/epidemiology’, ‘Oncology service’. Literature search was conducted through MEDLINE using the search engine PubMed. The articles identified in the literature search were reviewed and included if the abstract and full text were relevant to the research topic. Additional literature was found using the ‘similar articles’ function on PubMed. Further research articles were selected from the bibliography of reviewed articles. Additional studies were identified from the relevant references in the selected studies via manual search on LitCovid, Eurosurveillance, Elsevier, Lancet, Wiley Library, International Journal of Public Health, and BMJ journal websites.

Further, due to the emerging situation of the pandemic, reports from sources such as UK’s official government websites (NHS and ONS), Public Health Scotland (PHS), Public Health Wales (PHW), Northern Ireland Statistics and Research Agency (NISR), Centers for Disease Control and Prevention (CDC), European Center for Disease Prevention and Control (ECDC), European Mortality Monitoring (EuroMOMO), Institute for Health Metrics and Evaluation (IHME), Organization for Economic Co-operation and Development (OECD), Our World in Data, World Health Organization (WHO0, Cancer Research UK (CRUK), and The Health foundation UK were included to provide credibility to the discussion. Published guidelines and reports helped to compare healthcare policies initiated to prevent the spread of the pandemic. A few news journals that facilitated the discussion were also considered to maintain the continuity of the information provided.

All the selected studies in the literature search were reviewed for titles and abstracts. Only those studies relevant to the research topic were included in this review to discuss the direct and indirect impact of COVID-19 on the cancer care pathway in the UK. A search on the PubMed database showed many relevant articles out of which 17 were included after reviewing the title and abstract of the articles. These 17 articles were included after a full-text review. Manual searches through reference lists of included articles resulted in the identification of 40 more articles leading to a total of 57. All search results are included in Appendix II.

The search range for this review was broad. Research articles from the year 1963 to 2022 were reviewed to provide a thorough understanding of the concept of excess mortality, its methodology, and its application during previous pandemics and the current pandemic. For the statistics on excess cancer deaths in the UK, available data until the end of the year 2020 was considered. All included articles were explored for information on the incidence, epidemiological characteristics of COVID-19 and its variants, clinical features, risk factors for mortality, analysis of all-cause mortality during the pandemic, comparison of excess mortality between countries, and policy implications.

To understand the direct effects of the pandemic on cancer care services in the UK, UK’s four countries’ public health and cancer registry websites were explored. Further observations from policy briefs and published literature were synthesized to support the findings. The indirect effects of the pandemic on the cancer care pathway were explained based on the available data on three routes to diagnosis - screening pathway; diagnosis via GPs Two Week Wait (TWW) referral; and emergency presentation or hospital admissions during the pandemic. Furthermore, the decline in the quantity of cancer diagnostic procedures and treatments compared to the pre-pandemic period was explained based on the data available from the official statistics and reviewed literature.

6 Results

6.1 Excess deaths in the UK

The impact of the COVID-19 in all four nations of the UK was not similar. Between 29th February and 12th June 2020, the registered number of deaths from all causes and excess deaths was significantly high in England compared to its counterparts. Next to England, Scotland reported a greater number of deaths followed by Wales and Northern Ireland (Table 5) (116).

Table 4: Registered number of deaths and Excess deaths (based on the five-year average 2015-19) in the UK from 29th February to 12th June 2020

	England	**Scotland**	**Wales**	**Northern Ireland**
Deaths from all causes (2020)	198,794	21,169	11,852	5,353
Five-year average	142,217	16,284	9,679	4,503
Total Excess deaths	56,577	4,885	2,173	850
Excess deaths in %	39.8	30.0	22.5	18.9

Source: Adapted from Technical Advisory Group: Examining deaths in Wales associated with COVID-19 (116)

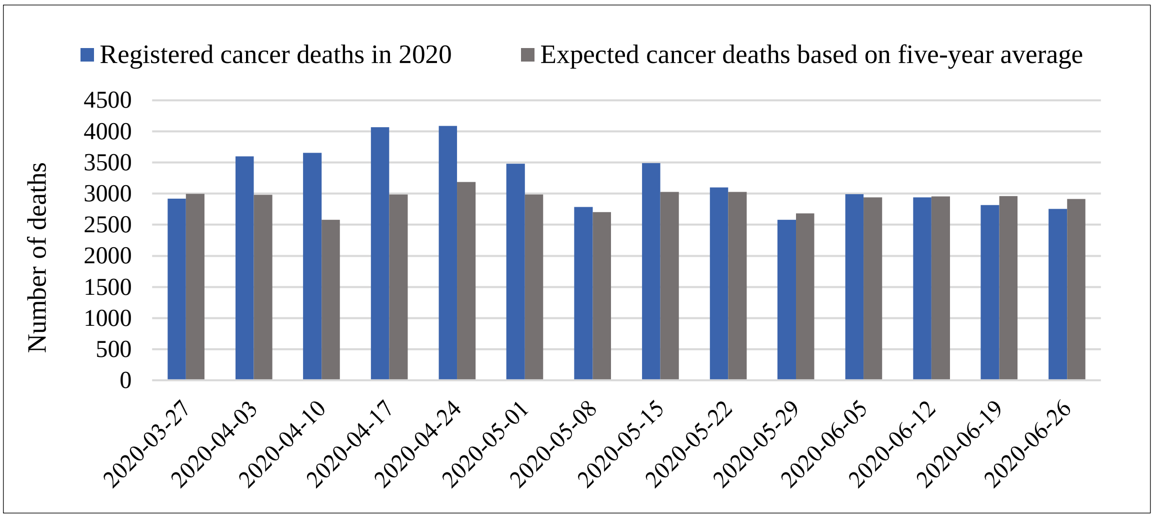
6.2 Direct impact of COVID-19

6.2.1 Excess Cancer deaths

Earlier studies have shown that patients with active cancer are at high risk of hospitalization with COVID-19 (117). However, age, gender and underlying comorbidities play a significant role in determining the survival outcome of cancer patients with COVID-19 (118). Also, the possibility of premature death among cancer patients with COVID-19 depends on the type of tumour (119).

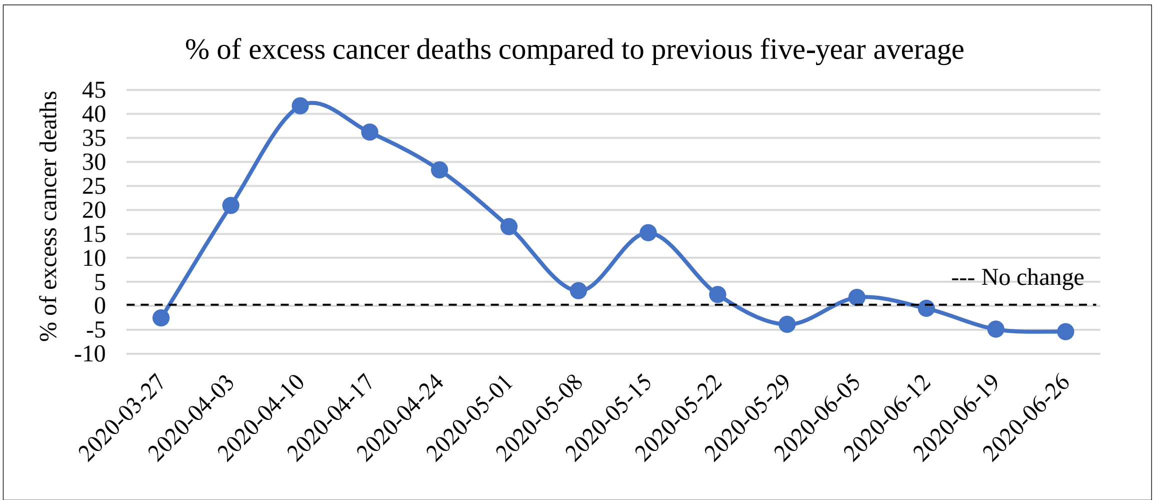
In England: Observations based on the data from the Office for the Health improvements and Disparities, England in the year 2020 (from the week ending 27th March until the week ending 25th December) showed that both excess numbers of deaths from all causes and the registered number of cancer deaths were high in England during initial weeks of the pandemic. Figure 4 shows the comparison of the registered number and expected number of cancer deaths between March and June 2020. From the week ending 27th March until the week ending 26th June, the number of registered cancer deaths was 45,272 which was 4,339 deaths above the expected number of cancer deaths based on the previous five-year average (2015-19). Excess cancer deaths were observed in the weeks ending 3rd April, 10th April, 17th April, 24th April, 1st May, 8th May, 15th May, 22nd May, and 5th June at 1075, 1080, 902, 492, 84, 461, 71 and 51 respectively. This represents an excess of 20.88%, 41.67%, 36.14%, 28.32%, 16.47%, 3.11%, 15.21%, 2.35% and 1.73% above the five-year average. On contrary, negative excess was noticed in the weeks ending 29th May (-3.87%), 12th June (-0.54%), 19th June (-4.89%), and 26th June (-5.42%) (Figure 5) (120).

Figure 2: Registered cancer deaths between March and June 2020 and expected cancer deaths based on the previous five-year average (2015-19) during the same period in England



Source: Adapted from Excess mortality in England and English Regions (120).

Figure 3: % excess cancer deaths between March to June 2020 compared to the previous five-year average (2015-19) during the same period in England

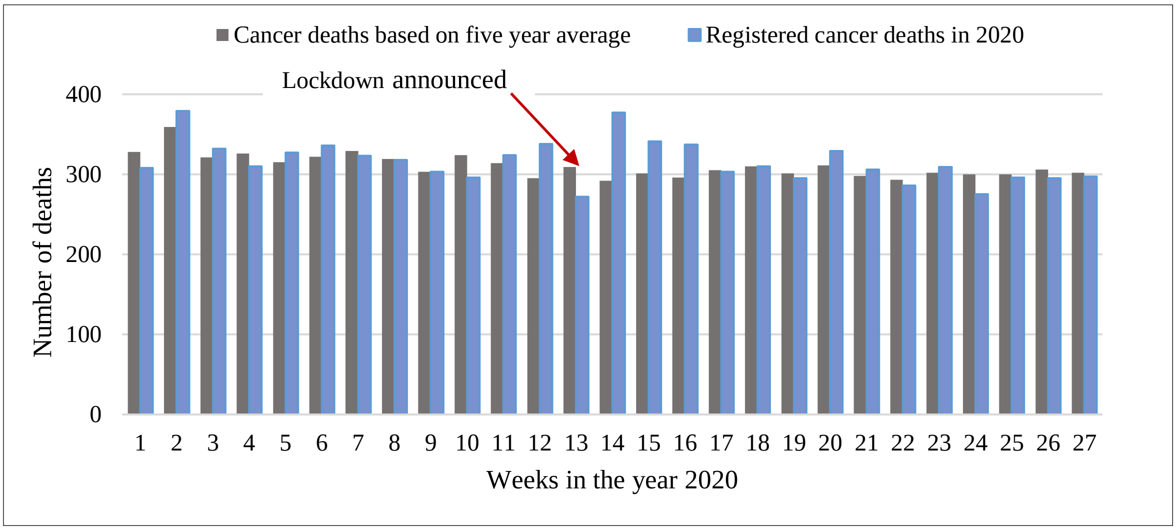


Source: Adapted from Excess mortality in England and English Regions (120) with additional calculations

In Scotland: Between March and June 2020, registered deaths from all causes were more than 20 thousand in Scotland. From the week the lockdown was announced (week 13th, 23rd March) until the end of June, 4,628 cancer deaths were registered (121). According to the data from the National Records of Scotland on deaths involving COVID-19 in the year 2020, the trend in registered cancer deaths was fluctuating until the end of June.

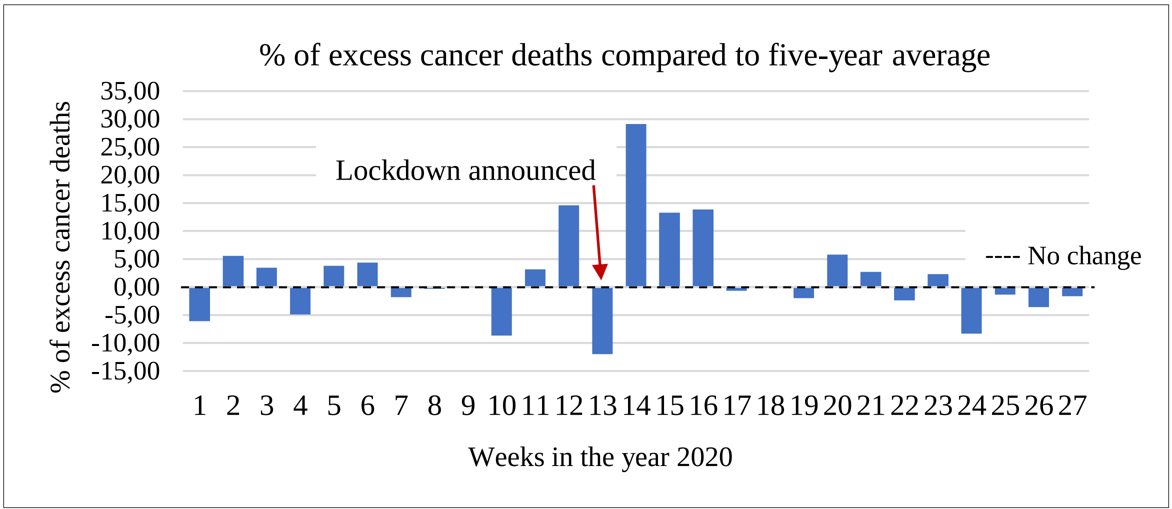
In weeks 14, 15, and 16, 377, 341, and 337 cancer deaths were registered respectively. This represents an excess of 29.11%, 13.29% and 13.9% of cancer deaths in weeks 14, 15, and 16 respectively compared to the corresponding five-year (2015-19) average. A period of no change (equal to a five-year average) and negative excess deaths were observed in weeks 17, 18, and 19. This period was followed by a few excess deaths 18, 6, and 7 in weeks 20, 21 and 23 respectively and negative excess was observed in further weeks until week 27 (Figures 6 and Figure 7) (122).

Figure 4: Registered cancer deaths between March and June 2020 and expected cancer deaths based on the previous five-year average (2015-19) during the same period in Scotland



Source: Adapted from National Records of Scotland (122)

Figure 5: % excess cancer deaths between March to June 2020 compared to the previous five-year average (2015-19) during the same period in Scotland



Source: Adapted from National Records of Scotland (122) with additional calculations

In Wales: Registered deaths from all causes from 29th February until 12th June were 11,852. Of which 2,436 (19.8%) deaths were attributed to COVID-19. During the same period, there were 2,173 excess deaths which represent 22.5% above the five-year average (116). According to the data from COVID-19 Recovery Profile by Public Health Observatory Wales, unlike England and Scotland, excess cancer deaths in Wales were low (61 deaths) between March and June 2020.

Compared to the five-year average there were 82.8 and 58.8 more cancer deaths in March and April 2020 respectively followed by a negative excess in May at -118.6. Again, in June 2020, 38 more cancer deaths were observed. However, rather than cancer, there were more excess deaths due to Dementia and Alzheimer's disease and nervous system diseases other than Alzheimer's, 186.2 and 72.8 respectively above the five-year average (123).

In Northern Ireland: There were more than 800 excess deaths between March and May 2020 which was 23% more compared to the previous five years' average (2015-19). Of the 894 excess deaths, 706 deaths mentioned COVID-19 as the underlying cause of death. During the same period, 75 excess cancer deaths were observed which was 6.8% higher than the previous five-year average. Causes such as diseases of the circulatory system (1.7%), Dementia and Alzheimer's (13.1%), and other causes (4.6%) have contributed to excess deaths. In contrast, diseases of the respiratory system have seen a negative excess -14.3% (124).

6.2.2 Estimated excess deaths, QALYs loss and economic impact due to delayed cancer services

Based on the hypothesis that the observed number of excess cancer deaths during the first pandemic wave would not have occurred under normal circumstances, many researchers from the UK have forecasted the impact of delayed cancer diagnosis and treatment on excess mortality, quality-adjusted life years (QALYs), life years lost (YLLs), also the economic loss. Surprisingly, the impact of delayed cancer care services was greater than the direct deaths. Studies that assessed the above impacts have been summarized in table 6 (119) (125) (126) (127).

Table 5: Estimated excess deaths, quality-adjusted life years lost, life years lost and economic impact due to delayed cancer services in the UK

Author, Year	Method of the study	Purpose of the study	Types of cancer studied	Results
Gheorghe et al (May -2021) [125]	Nationwide Population-based modelling study	The economic impact of avoidable cancer deaths due to diagnostic delays and additional QALYs	Brest, Bowel, Lung, and Oesophagus	• Productivity losses are estimated to be 103.8milllion GBP for all four cancers over five years • QALYs lost due to excess cancer deaths across four cancers would be 32,700 over five years
A. Sud (May -2020) [127]	Observational study	Impact of 3 and 6months delay in cancer surgery on LYG[1] based on 5year survival	31 cancer types/subtypes according to cancer stage and age at diagnosis	• 4,755 and 10,760 excess deaths would occur over one year upon three months delays and six months delays in cancer resection. • LYG[1] reduction by 17.1 and 15.9 for three months delay and six months delay respectively.
Camille Maringe (Jul -2020) [119]	Nationwide Population-based modelling study	Cancer diagnostic delay on survival impact in 1, 3 and 5 years	4 cancers - Breast, Cervical, Lung, Oesophagus	• 3,291 to 3,621 avoidable cancer deaths and 59,204 to 63,229 YLLs[2] were attributable to delayed cancer diagnoses
Alvina G Lai (Nov -2020) [127]	Cohort study	Impact on cancer services and excess 1-year mortality	24 cancer types	• estimated 7,165 to 17,910 excess deaths over one year assuming 40% of cancer patients will be affected in the long-term • nearly 80% of excess deaths in cancer patients with one comorbidity

[1] Life years gained; [2] Years of life lost

6.3 Indirect effects of COVID-19 on cancer care services diagnosis

By identification and categorisation of the patient's paths to cancer diagnosis, any survival variation on various routes to cancer presentation can be determined. Following are the eight routes to cancer diagnosis identified in the UK - Screen-Detected; Death Certificate Only (DCO); emergency; two week wait (TWW) referral; GP referral; inpatient elective; outpatient; and unknown (no data available from inpatient or outpatient HES, cancer waiting times (CWT) and screening) (128). In this review, the indirect effects of the pandemic on cancer care were explained based on the available data on four routes to cancer diagnosis.

6.3.1 Screening services

During the first wave of the pandemic, nearly three million individuals in the UK were not able to participate in the bowel, breast and cervical cancer screening programs because the services were with-held due to the risk of coronavirus (129). **In England**, routine cancer screening programs for breast, cervical and bowel cancers were paused between March and June 2020. It was estimated that a million bowel cancer invitations were postponed.

Screening services were resumed in mid-April for women who were at very high risk of breast cancer and routine screening for all eligible populations was resumed in June/July 2020. However, due to the pandemic, data collection on breast screening patterns in 2020/21 was impacted (130). Unlike breast and bowel screening, the effect of the pandemic on cervical screening programs was minimal. After resuming the services, the number of screening tests quickly reached the pre-pandemic level (131).

In Scotland, the age-adjusted cancer registration rate fell dramatically by more than 500 per 100,000 persons in the year 2020. This analysis was based on comparison with the previous years from 2010 to 2019. The decrease in cancer incidence among five cancers, cervical, colorectal, breast prostate, and lung cancers was at 24%, 19%, 11%, 10% and 7% respectively compared to the preceding year. These reductions can be linked to the halted screening programs. As the breast screening program was halted at the end of March 2020, for a period of two months, there was a 39% drop in breast screening program registrations (132).

In Northern Ireland, routine cancer screening programs for bowel, breast, and cervical cancers were suspended temporarily on 7th April for a period of three months (133). Estimation of the impact of COVID-19 on cancer diagnosis by the Northern Ireland Cancer Registry (NICR) shows that the incidence of bowel cancers diagnosed (by pathology samples) through screening tests among those aged 60-74 years fell by 52% and 57.1% in April and May 2020 respectively corresponding to the monthly averages in the years 2017-19. Also, the incidence of breast cancer among females aged 50-70 years through screening dropped by 30% in April and 55.9% in May and 25% in June in comparison with the 2017-19 monthly averages (134).

In Wales, according to the analysis of Wales cancer data by DATA-CAN Cancer Collaboration Cymru (DATA-CAN CCC) between 2019 and 2020 revealed that the overall incidence of three cancers (breast, bowel, lung) was decreased by 15% in 2020 compared to the incidence in the year 2019. Breast cancers diagnosed through screening programs were the most affected representing a 48% decline and a substantial decline of 86.7% was noticed in the months from April to June. Also, breast malignancies being detected in stage I decreased by 41.6%. In contrast, unknown stage breast cancer diagnosis increased by 55.8%. Whereas the decline in colorectal cancer incidence through the screen-detect pathway was only 13.3%. This could be because of the initiation of faecal immunochemical testing (FIT) and delivering FIT kits to home (135).

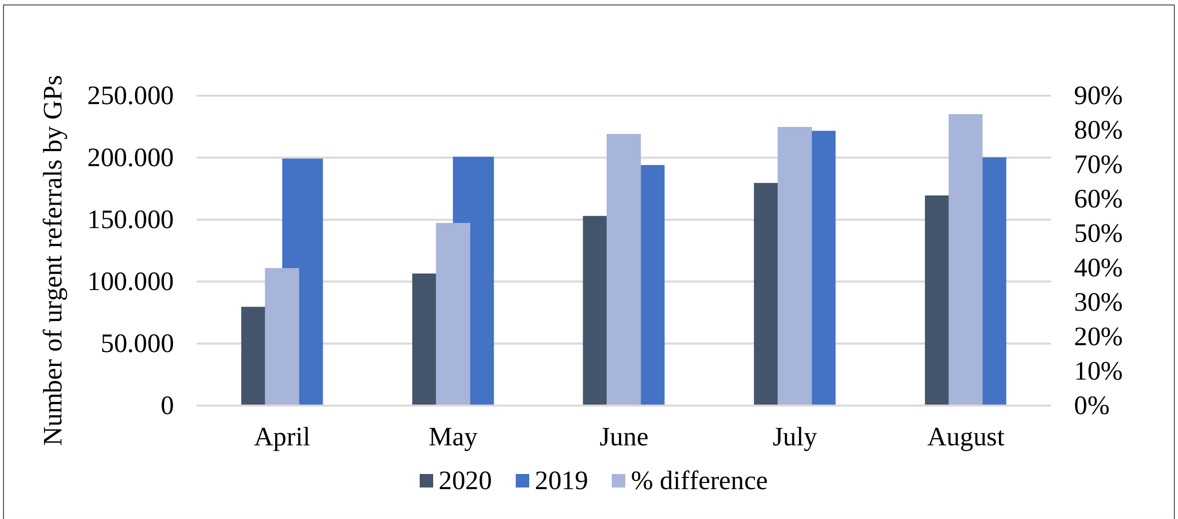
6.3.2 Primary care referrals to cancer specialist care during COVID-19

Generally, in England, GPs refer patients with possible signs or symptoms of cancer to the specialist via urgent two week wait (TWW) cancer referral according to the National Institute of Health and Care Excellence guidelines. Most cancers are diagnosed through this way followed by routine GP referral and emergency presentation (136). The number of GPs' urgent TWW referrals fell dramatically. In April 2020 there were more than 100,000 fewer referrals compared to the number of referrals in April 2019 (137). The reduction was also seen in the number of GP consultations (> 20 million in April 2019, and 16 million in April 2020) (138).

In England, during the pandemic, the proportion of GP-urgent referrals fell by 40% in April, 53% in May, 79% in June, 81% in July and 85% in August which represents 327,777 fewer patients were referred to specialist consultation by GPs in 2020 than in the preceding year (Figure 8) (139). In Wales, between April and June 2020, bowel cancers and non-small cell lung cancers diagnosed through GP-urgent suspected cancer care pathways reduced dramatically by 50.3% and 53.9% respectively compared to similar months in the year 2019. In contrast, the reduction in GP urgent referrals for breast cancer was minimal at 0.4% and after June, the services were quickly resumed to over 2019 levels (135).

Furthermore, diagnostic procedures performed to detect cancer particularly endoscopic services were severely impacted. Majority of the gastroenterology societies in the pandemic affected countries published guidelines for halting non-urgent endoscopic procedures. These guidelines impacted cancer diagnostic care pathways including bowel screening and surveillance (140).

Figure 6: GP two week wait urgent cancer referrals to first specialist consultation in England in 2019 and 2020



Source: Cancer Waiting Times- National Time Series October 2009 – June 2022 (139)

Rutter M et al. conducted a study in the UK including 4 nations and regions of England to analyse the impact of the pandemic on four endoscopic services (colonoscopy, flexible sigmoidoscopy, esophagogastroduodenoscopy (OGD) and endoscopic retrograde pancreatography (ERCP) and decline in upper and lower Gastrointestinal cancer diagnosis. Their analysis found that the number of cancers detected through endoscopic procedures dropped to an average of 283 per week during pandemic impacted week (23 March to 31 May) compared to an average of 677 per week during the pre-pandemic period (16 January to 15 March). Also, procedures conducted per cancer decreased to 15 in the COVID-impacted period from 52 during the pre-pandemic period. (141).

6.3.3 Emergency presentation and hospital admissions

In addition to suspended routine screening programs and a decline in GP referrals, fluctuation was also noted in the number of cancer patients presenting via the emergency department. Earlier studies from England on the 1-year relative survival of cancer patients via routes to diagnosis revealed poorer outcomes of cancer patients presenting to the emergency department than other routes to diagnosis (128). In England, between March and August 2020, the proportion of emergency admissions was below 22% more than in the year 2019. Data from the years 2018-19 shows that an estimated 6000 fewer cancers were diagnosed in 2020 upon emergency presentation (142).

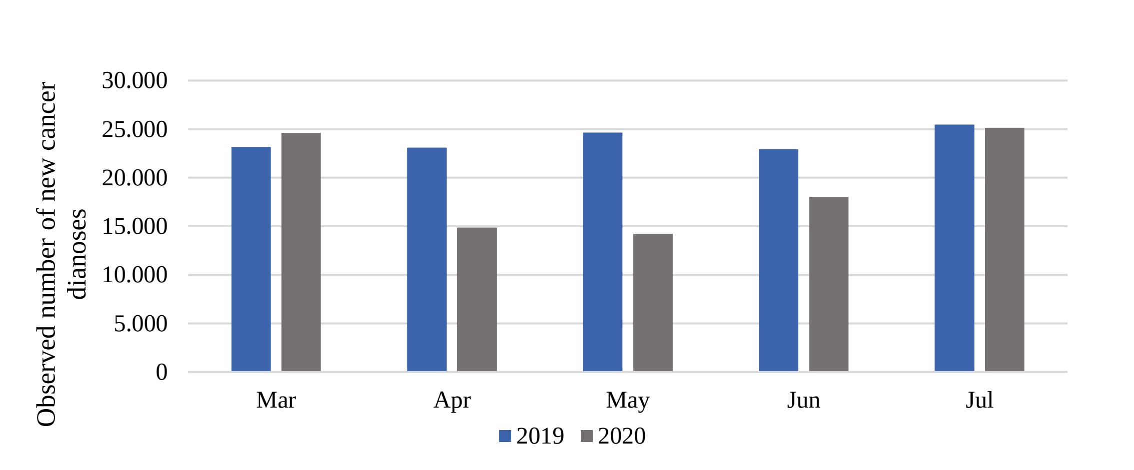
Before the pandemic, the proportion of cancers diagnosed upon presentation to the emergency department was estimated to be 20%. A population-based survey on the impact of the pandemic on emergency cancer admissions in Northern Ireland (comparing the data from March to December 2020 to similar months in the years 2017-19) showed that there was a 12.3% reduction in emergency cancer admissions with the marked highest drop in the months of April and October at 18.5% and 16.8% respectively (143).

A study on the impact of lockdown due to the pandemic on non-COVID-19 conditions (cancer, cardiovascular and respiratory) in the UK revealed that cancer related hospital admission rates were 14.8% and 10.6% less in Scotland and Wales respectively during the post-pandemic period (between August and September) compared to the levels in years 2016-19. Whereas, in England cancer related hospital admission rate was 14.3% less compared to similar months in the year 2019 (144).

Based on the above observations, reports indicate that there was a relative decline in the overall cancer incidence in the UK during the first pandemic wave. Data from the rapid cancer registry, in England, shows that in April, May, and July 2020 the number of new cancer diagnoses decreased by 8,223, 10,408, 4,898, and 313 respectively compared to corresponding months in the year 2019 (Figure 9) (145). In Scotland, the overall number of new cancer cases reported in the year 2020 was 30,395 which was 33,156 in the year 2019 (132).

In Wales, a study on the impact of the pandemic on colorectal, breast and non-small cell lung carcinoma based on the data from the cancer clinical record system in 2019 and 2020 reported that the overall incidence of all three cancers reduced by 15.2%. The incidence rate ratio of female breast cancers was 0.81% (95% CI: 0.76–0.86, $P < 0.001$), 0.80% for colorectal cancers (95% CI: 0.79–0.81, $P < 0.001$) and 0.91% for non-small cell lung cancers (95% CI: 0.90–0.92, $P < 0.001$). These reports indicate that there was a decline in cancer incidence. However, it is difficult to ascertain that the decline occurred due to a smaller number of actual cancer cases occurring or due to the hindrances in the cancer care pathway during the first pandemic wave (135).

Figure 7: Cancer incidence in England in 2019 and 2020



Source: Adapted from NCRAS (National Cancer Registration Analysis Service), England (145)

6.3.4 Impact on cancer therapy

During the first wave of the pandemic, elective operations were cancelled worldwide in response to COVID-19 mitigation measures and because of the patient's risk of developing post-operative complications. Mobilizing the health care resources to manage COVID-19 patients further impacted continuing many elective surgeries. These elective surgeries also include cancer surgeries (146). Although the professional bodies in oncology care issued guidelines on the safe handling of the procedures, still many countries postponed or cancelled cancer operations. For example, in Australia, all AHMAC Category 3 procedures (i.e., procedures which can be performed within a one-year duration) were cancelled. In New Zealand, from 24th March 2020, most of the elective surgeries (i.e., all nonacute planned and all non-urgent cancers) were cancelled (147).

NHS England paused all elective surgeries including cancer from mid-April 2020. Also, the routine cancer treatment pathway was modified to minimise hospital visits and risk of virus exposure such as the provision of repeat oral medication prescription, at-home treatment, and home delivery of medication (148). Data from the National Cancer Registration and Analysis Service, in England, shows that the monthly radiotherapy episodes in April, May and June were down by 75% and 89% of 2019 levels respectively (149). The proportion of systematic anti-cancer therapy (SACT) also declined by 83% and 75% of the 2019 level in April and May 2020 respectively (150).

A study on the impact of COVID-19 on SACT by obtaining real-time data on the number of patients attending SACT in NHS Scotland revealed that between 2nd March and 19th April 2020 the number of patient attendances reduced by 28.7%. In April 2020 alone, there was a 17.2 % decline compared to the corresponding month in the year 2019. Bowel cancers have seen the largest decrease in attendance by 43.4% followed by lung cancers by more than 30% and haematological cancers by 30%. In contrast, the reduction in breast cancer attendance was below 20% and recovered quickly in the subsequent period. However, there was no noticeable difference in improvement in the SACT episodes for other malignancies (118).

Findings in a nationwide observational cohort study to estimate the reduced volume of surgical activity in 2020 in NHS England and Wales showed that there was a 33.6% drop in surgical activity corresponding to the previous four-year average (2016-19) (151). In a survey by the Royal College of Surgeons Edinburgh in the year 2020, among 15,000 cancer surgeons in the UK revealed that 33%

of the surgeons completely stopped cancer operations and 87% reduced them. More than 50% mentioned that 'COVID-free hubs' were not yet established by the NHS trust (152).

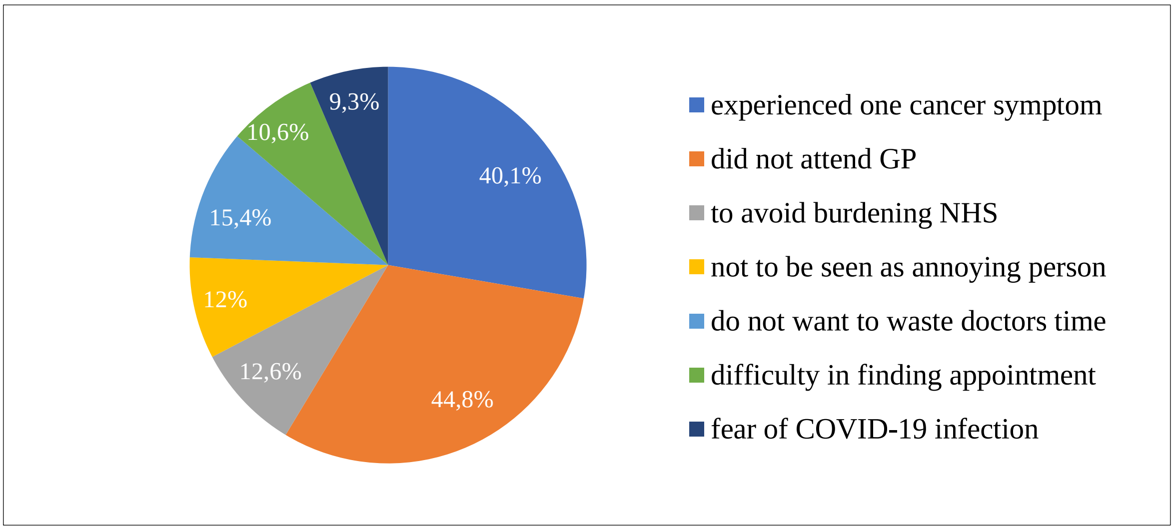
A systematic literature review and metanalysis on the mortality impact of delay in cancer treatment revealed that there is a strong association between a high risk of death and delay in radiotherapy, systematic anti-cancer treatment and surgical intervention of head and neck, breast, lung, cervix, colon, rectum, and bladder cancers. Also, the study findings showed that each 4 week delay in surgical intervention results in a 6-8 fold increase in mortality (153). Furthermore, NHS faced a shortage of workforce to continue routine oncological services while prioritizing the resources to manage an increasing number of COVID-19 patients. COVID-19 infected staff, self-isolation, and limited resource availability further impacted the continuity of cancer care (154).

6.3.5 Changes in the help seeking behaviour of cancer patients due to pandemic

NHS guidelines stated that physicians should continue providing urgent and essential care for cancer patients. Despite the availability of cancer care services, there was a decline in the number of patients seeking cancer care services due to decline in GP referrals, and long waiting times from physician to specialist consultation. Compliance with social distancing measures and concerns over the risk of contracting the virus also influenced the health seeking behaviour of cancer patients. Earlier studies have reported the association between the prevalence of cancer symptoms and help seeking behaviour of cancer patients (155) (156).

Between August and September 2020, Cancer Research UK and Cardiff University conducted a prospective, mixed-method observational cohort study on help seeking behaviour and attitudes towards COVID-19 (from March to August 2020) including 7,543 participants from the UK. The findings revealed, 40.1% of the participants experienced at least one cancer symptom during the pandemic. Surprisingly, nearly 44.8% of the participants did not attend GP despite observing possible cancer symptoms such as haemoptysis. Other barriers and attitudes to health seeking behaviour are shown in figure 10.

Figure 8: Cancer symptoms and help-seeking behaviour and attitudes during the pandemic in the UK



Source: adapted from Quinn-Scogins, Harriet D et al.
Cancer symptom experience and help-seeking behaviour during the COVID-19 pandemic in the UK: a cross-sectional population survey (157).

Qualitative interviews of the 30 participants of the study revealed that the change in their health status was due to existing underlying comorbidities but cancer was not the reason for deferring physician consultation in most of the participants. All participants expressed fear of exposure to the virus at healthcare facilities and people who do not follow social distancing measures. Adapting new changes in the health care practices such as remote consultations influenced health seeking behaviour. However, those who consulted GP were satisfied with the quality of care and remote consultation they received and many were in favour of continuing remote consultations alongside face-to-face in the future (157).

Further, many cancer patients were concerned that during the COVID-19 crisis, their treatment was overlooked. A survey conducted by Cancer Research UK (CRUK) to analyse the impact of the pandemic on cancer care pathways revealed that nearly 40% of the testing plan and more than 30% of the treatment plan were disrupted since the time lockdown was reinstated. Around 60% of the survey participants mentioned that their cancer care was better during the pre-pandemic period. Furthermore, a significant proportion of patients mentioned that they feel frustrated (72%), anxious (68%), and afraid (59%) when they were asked about their response to modified oncological services. Moreover, 68% of the participants were not informed regarding new appointments for cancelled or postponed services (72).

6.4 Remote consultation and challenges

Digital consultation in primary and outpatient care in the next five years was one of the milestones set up by NHS (158). However, during the pandemic, e-consultations became a necessity to limit the spread of the virus across the country. Many routine face-to-face consultations were converted to remote and digital outpatient treatments (159). NHS Digital statistics show that there was a significant reduction in the demand for primary care services and GP appointments during the lockdown.

However, GP telephone consultations have risen significantly (160). This might have impacted the early detection of cancer symptoms and the long waiting periods for specialist consultation. Also, thorough clinical assessment, for example, a physical examination which suggests possible cancer is likely to be compromised due to virtual consultation leading to delay in diagnosis and treatment in cancer patients (161). Nevertheless, it was challenging to collect the data and estimate the impact of these remote consultations on access to primary care because of COVID-19 (160).

A qualitative study by Stephanie Archer et al on GPs' view of the impact of covid on clinical assessment of possible cancer in primary care in the UK revealed that remote consultation instead of face-to-face visits contributed to mitigating the risk of contracting COVID-19. However, due to the pandemic, there was an abrupt transformation (routine face-to-face consultation to telephone, e-mail, and video consultation) in the healthcare practice, which most of the participant GPs expressed concern about. A possible consequence of these changes might be compromised in both safety and effectiveness in the primary health care system. Also, these changes have contributed to delayed cancer diagnosis, particularly for those patients who may not be able to convey their symptoms on the telephone. Limitation in the usage of these modified services is also seen among people living in rural areas with poor connectivity (161) (162).

7 Discussion

This study explored the concept of excess mortality that includes deaths both directly and indirectly attributed to COVID-19. However, many countries have difficulty estimating excess deaths as a routine practice. This is because most of the COVID-19 deaths were either not reported or subject to delays in reporting. Moreover, at the global level, only 68% of countries have well-established public health threat surveillance systems and over 66% of low-income countries still do not have a standardized cause-of-death reporting system (163).

This literature review also revealed that there was excess mortality, directly and indirectly, caused due to COVID-19 in the UK. Particularly, the number of excess deaths was high in England and Scotland followed by Wales. Excess deaths were low in Northern Ireland (116). Furthermore, the number of excess cancer deaths was also high in England compared to other UK countries during the initial weeks of the pandemic (from the week ending 3rd April to the week ending 15th May 2020) (120). The emerging situation of the pandemic has led to the implementation of a lockdown to limit the further spread of the infection (164). However, while this facilitated heightened protection for the public against further COVID-19 infection, it led to significant delays in the oncology care services. This would have contributed to indirect mortality among cancer patients due to COVID-19.

Early in the pandemic, Cortiula et al emphasized the ‘distraction effect’ caused by the re-deployment of all care services towards the pandemic. This might incur negative consequences and providing timely services was overshadowed particularly for patients with cancer who benefit from timely intervention (165). For instance, an estimated three million people in the UK did not receive screening invitations for bowel, breast and cervical screening programs during the first lockdown period (129).

Delays in the cancer screening tests might lead to cancers being detected at a much later stage where cancer has spread to distant organs (i.e., metastasized) causing severe implications that are hard to treat and recover from. Some tumours present with an insidious growth which is usually diagnosed by regular screening. However, disruption in screening services would impact the detection and treatment of these tumours and renders it challenging to measure the impact of delayed screening services on cancer prognosis (166).

7.1 Mitigating efforts to continue cancer care during COVID-19

7.1.1 Cancer screening services

Earlier evidence shows that NHS cancer screening programs detect a major proportion of cancers and account for preventing many deaths due to cancer (167). These guidelines would have been given a high priority while pandemic policies were sought thereby many avoidable cancer deaths would have been prevented. Although cancer services were reportedly given priority, the number of patients approaching primary care services was less due to fear of contracting the virus and to comply in response to nationwide social distancing measures (119). These reasons could imply, nearly 2,300 cancer cases are left undiagnosed each week resulting in a bulge in the waiting list and leading to disease diagnosis at an advanced stage challenging the chance of survival outcomes for cancer patients (168). Moreover, while meeting the standard healthcare demands, providing extra capacity for the extended waiting list will be challenging (169).

7.1.2 Cancer referrals, diagnosis, and treatment services

In England, the decline in GP urgent two week wait referrals for suspected referrals from March to August 2020 was ranging between 40% to 85% compared to the levels in the preceding year (139). In Wales, between April and June 2020, GP urgent referrals for both bowel and non-small lung cancer reduced by just above 50% of the 2019 levels (135). The overall impact of the pandemic on cancer diagnostic services is reflected in a fall in the incidence of cancer in the UK between March and May 2020. The decline in the number of new cancer diagnoses during the first pandemic wave was also seen in other European countries such as France (170), and the Netherlands (171).

During the pandemic, the cancer treatment pathway was modified to minimise hospital visits, risk of exposure to the virus and post-therapeutic complications considering the immunocompromised status of cancer patients. Consequently, oncologists have had delayed or reduced SACT for certain cancers emphasizing the benefit of delayed or suspended therapy compared to the risk due to limited scientific evidence. However, these decisions were based on the probability of a high risk of infection and the prediction of certain complications that might not be favourable in all circumstances (172). Hence, a decline in radiotherapy and chemotherapy attendance was noticed during the first pandemic wave (118) (149) (150). This signifies the importance of the availability of scientific evidence that can aid in prompt decision making and appropriate clinical guidelines during public health emergencies.

Furthermore, many elective cancer surgeries were cancelled or postponed during the early weeks of the pandemic. Each four week delay in surgical intervention results in a six to eightfold increase in the risk of mortality (153). Although covid hubs were arranged to line up elective cancer surgeries, information on the available testing capacity to detect COVID-19 ensuring safety among patients and the staff in those cancer hubs was lacking. Moreover, the focus of these hubs was limited to cancer patients requiring surgical intervention (173) (174).

To encourage patients to utilize care services, NHS deployed information campaigns to project that NHS is rolling urgent and emergency care for non-covid patients who are in need. Also, enhanced 111 online service capacity, prioritized cancelled appointments, and restarted maternity service and immunization and cancer services. The decision of rolling out these information campaigns was based on a reduction in the number of admissions to accident and emergency (A&E) with cerebrovascular and myocardial infarction. However, it was not clear whether these campaigns include people with early cancer warning signs. Moreover, the utilization of these services by the patients in compliance with non-pharmacological interventions was a major concern due to the fear of contracting the virus (175) (176).

7.1.3 The estimated long-term impact of delayed services

The overall impact of the disruption in the entire cancer care pathway during the pandemic resulted in excess cancer deaths in the UK, particularly in England. According to ONS estimates in July 2020, the long-term impact of delayed cancer diagnosis via GP referrals or emergency visits (across 18cancer types) would cause 1,400 excess cancer deaths, 3,500 QALYs loss and 4,900 YLL which represents an underestimation of the overall impact and could be misleading because they were based on the review of the published literature. Moreover, these estimates were based on the data from England and extrapolated to the overall UK (177). Careful and precise assessment of the data on the delayed cancer diagnoses from all four nations of the UK might help in effective decision making thereby preventing excess deaths in the future. Early assessment of delayed diagnostic services due to the pandemic, might also avert the economic impact due to these avoidable cancer deaths.

7.1.4 Telehealth services

Digital consultation in primary and outpatient care in the next five years was one of the milestones set up by NHS (158). During the pandemic, e-consultations became a necessity to limit the spread of the virus across the country. Therefore routine face-to-face consultations converted to remote and digital outpatient treatments (159). Consequently, GPs' telephone consultations had risen. However, the main drawback of this service was physicians were not able to perform clinical assessment which suggest signs of cancer through consultations. Despite the limitation, the advantages of telehealth for cancer patients have minimised hospital visits, convenience, time and cost savings (178).
Although, it cannot substitute physical care the benefit of this service particularly for cancer patients to provide continued care services in times of pandemic should be prioritized. Therefore, research in this aspect highlighting the use of telehealth and its benefits as complementary to the existing care services for cancer patients is needed.

While the struggle to combat the first wave continues, most experts warned about a second winter wave, and to prepare for continued health care services at an increased capacity alongside following non-pharmacological interventions. UK's cancer care services were not recovered to the pre-pandemic level despite dire warnings, required preparation time and available evidence on the impact of delaying cancer diagnosis and treatment. For example, the surgical care pathway for head and neck cancers (H&N) during the second wave was impacted to a great extent compared to the first wave in the UK. New H&N cancer referrals reached 80% to more than 100% of the pre-pandemic level however, radiotherapy and surgical services were compromised (179).

7.2 Limitations

This literature review is based on the published literature explaining the mortality burden of the pandemic and disrupted cancer care services in the UK during the first pandemic wave. The methodological quality of this review was compromised because the articles included were not evaluated for validity. This review did not acknowledge the information on excess deaths estimates at specific location settings (community, care homes, prisons). Another limitation is that while discussing the disruptions in the cancer care pathway, the focus was more on England rather than the four countries of the UK. This was because the weekly excess mortality estimates are not available for Wales, Scotland, and Northern Ireland. This review included only one research article explaining the changes in the help-seeking behaviour of cancer patients towards health care and support during the pandemic in the UK. Because studies in this aspect were limited, further research should be conducted to enhance evidence-based recommendations that can inform public health policy and increase awareness among cancer patients.

8 Conclusion

This review of the literature showed that there were discrepancies in the measurement indices (variation in testing capacity, definition and reporting of COVID-19 deaths) across the nations. Hence, comparison of excess mortality across nations is essential to understand the effect of the policies implemented in various countries to reduce the mortality burden during the pandemic. Meticulous examination of the chronological reporting of the cause of death and other factors in the death certificate of those with comorbidities can help to disentangle the issue of underreporting of deaths to some extent. Hence, timely and comprehensive population data are essential.

There was high all-cause mortality and excess cancer mortality during the first pandemic wave in the UK particularly in England. This could be due to the interruption in care pathways leading to delayed diagnosis and treatment (indirect) or due to the higher vulnerability of cancer patients to COVID-19 infection causing severe morbidity and mortality (direct). While excess mortality can be used as a measure to understand the overall (both direct and indirect) mortality burden of the pandemic in cancer patients, it was difficult to ascertain which factors contributed more to excess mortality.

One might argue that this was the inevitable direct consequence of the pandemic on the already immunocompromised cancer patients leading to excess mortality. However, evidence from the literature showed that the interruptions in cancer care pathways and ineffective policies to control the pandemic further exacerbated this excess mortality. Additionally, changes in the health-seeking behaviour of cancer patients due to fear of acquiring infection in the healthcare setting could have contributed to delayed care leading to increased mortality.

Therefore, significant research regarding the use of excess mortality as a measure for precise assessment of the direct and indirect effects of the pandemic is crucial. Literature also shows that high excess mortality was due to the lack of preparedness of the healthcare system in dealing with the emergency situation of the pandemic. Consequently, expansion of health care resources, regular analysis and evaluation of executed policies are crucial for an equitable response to the pandemic situation.

There is a requirement for continuous surveillance of future health risks and effective programs for the improvement of developing pre-prepared tools that aid in mitigating the risk of morbidity and mortality due to the pandemic. Furthermore, the implementation of effective preventive policies that reduce the spread of the infection, increase preparedness to strengthen the health care delivery system and continued evaluation of the implemented policies would eventually reduce overall excess mortality during future pandemics.

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10 Appendix I

Summary of the studies on the excess mortality due to COVID-19 with various baseline historical data

Author	*Study population*	*Methodology*	*Reference period for baseline historical data*	*Results*
Alyssa Bilinski, Ezekiel J. Emanuel, 2021	The USA and 18 OECD countries with more than 5mill population	Poisson regression model	2015-2019	US had high COVID-19 mortality and excess all-cause mortality compared to other OECD countries
André Vieira et al 2020	Portugal with eight other European countries	Relevant excess mortality and ARIMA model	2015-2019	1255 (14%) more than expected excess all-cause deaths observed in Portugal
Annie Campbell and Sion Ward,2021	34 European countries	Weekly averages (5year average death counts and death counts)	2010 to early 2020	England & Wales, Spain experienced nearly 100excess deaths /100 000 people
Karlinsky and Kobak 2021	103 countries and territories	Including seasonal variation and yearly trends in mortality	2016 to 2019	More than 60% (69 out of 103) of countries showed significant positive excess mortality
Kontis et al 2020	21 industrialized countries	16 Bayesian model	past 10years	Significant excess deaths were observed in the age group >65years
Lasse S Vestegaard et al, 2020	EuroMOMO (24 European countries or Federal states)	Pooled analysis of weekly deaths	January 5, 2015 to January 25,2020	Excess all-cause deaths were 28% higher than reported deaths
Rizzi and Vaupel 2021	Denmark and Sweden	Short-term forecasting for 1 year	2015 to 2019	Sweden experienced more excess deaths (5447)than Denmark (604)
WHO	194 countries	Multinominal model+ Binomial Spline model	2000 to 2019 for annual mortality data/ 2015-2019 for monthly mortality data	14.9mill excess deaths for the years 2020 and 2021

11 Appendix II

PubMed search results							
	Search Terms	No. of articles in search	No. of relevant articles	No. of articles chosen in new search	No. of articles already chosen in previous search	No. of articles not chosen in new search	Comments after reviewing abstract
1	‘COVID-19’, ‘United Kingdom/epidemiology’	2,725	--	--	--	--	Further search terms will be added
2	‘COVID-19’, ‘excess Mortality’, ‘United Kingdom/epidemiology’	571	--	--	--	--	
3	‘COVID-19’, ‘excess Mortality’, ‘United Kingdom/epidemiology’, ‘Oncology services’	19	10	5	0	14	9 articles not relevant to the topic and 5 excluded after abstract screening
4	Using Search similar articles function in PubMed	158	12	12	5	146	146 articles not relevant to the research question after abstract screening
5	Bibliography search from included articles	65	40	40	17	25	25 articles not relevant to the research question after abstract screening
6	Reports and Statistical data from official websites (e.g., CDC, ECDC, OECD, NHS, ONS, WHO etc)*	22	-	-	-	-	-

*****because the pandemic situation was evolving, mortality statistics and data on the cancer statistics were obtained from the official government website