Epilepsy-related mortality during the COVID-19 pandemic: a nationwide study of routine Scottish data

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Abstract

Objective: To examine whether epilepsy-related deaths increased during the COVID-19 pandemic and if the proportion with COVID-19 listed as the underlying cause is different between people experiencing epilepsy-related deaths and those experiencing deaths unrelated to epilepsy.

Methods: This was a Scotland-wide, population-based, cross-sectional study of routinely-collected mortality data pertaining to March–August of 2020 (COVID-19 pandemic peak) compared to the corresponding periods in 2015–2019. ICD-10-coded causes of death of deceased people of any age were obtained from a national mortality registry of death certificates in order to identify those experiencing epilepsy-related deaths (coded G40–41), deaths with COVID-19 listed as a cause (coded U07.1–07.2), and deaths unrelated to epilepsy (death without G40–41 coded). The number of epilepsy-related deaths in 2020 were compared to the mean observed through 2015–2019 on an autoregressive integrated moving average (ARIMA) model (overall, men, women). Proportionate mortality and odds ratios (OR) for deaths with COVID-19 listed as the underlying cause were determined for the epilepsy-related deaths compared to deaths unrelated to epilepsy, reporting 95% confidence intervals (CIs).

Results: A mean number of 164 epilepsy-related deaths occurred through March–August of 2015–2019 (of which a mean of 71 were in women and 93 in men). There were subsequently 189 epilepsy-related deaths during the pandemic March–August 2020 (89 women, 100 men). This was 25 more epilepsy-related deaths (18 women, 7 men) compared to the mean through 2015–2019. The increase in women was beyond the mean year-to-year variation seen in 2015–2019. Proportionate mortality with COVID-19 listed as the underlying cause was similar between people experiencing epilepsy-related deaths (21/189, 11.1%, CI 7.0–16.5%) and deaths unrelated to epilepsy (3,879/27,428, 14.1%, CI 13.7–14.6%), OR 0.76 (CI 0.48–1.20). Ten of 18 excess epilepsy-related deaths in women had COVID-19 listed as an additional cause.

Conclusions: There is little evidence to suggest there have been any major increases in epilepsy-related deaths in Scotland during the COVID-19 pandemic. COVID-19 is a common underlying cause of both epilepsy-related and unrelated deaths.

Keywords: Seizures; Administrative data; SUDEP; Coronavirus disease 2019; Severe acute respiratory syndrome coronavirus 2; Fatality

1 Introduction

Epilepsy contributes to a substantial proportion of the global burden of neurological disease, affecting 50–70 million people wordwide.[1,2] In the United Kingdom (UK) alone, seizures are the most common neurological cause of unscheduled hospital admissions.[3] People with epilepsy (PWE) are at significantly increased risk of premature death.[4-8] Some of those deaths may be entirely unrelated to their epilepsy,[5,9] for example in an assault or a pulmonary embolism. In such cases, the epilepsy is not mentioned anywhere on the death certificate, in line with national death certification guidance.[10] A substantial proportion of the deaths in PWE, however, relate directly to the epilepsy itself (including sudden unexpected deaths in epilepsy (SUDEP), seizure-related accidents, or status epilepticus), or they can occur indirectly due to epilepsy (e.g. as a result of aspiration pneumonia after seizures).[5,11] Some deaths in PWE may also be associated with a concurrent fatal condition, such as comorbid viral infection triggering terminal seizures. In all such circumstances, epilepsy is mentioned either as an underlying or contributory cause of death in the death certificate, alongside the aspiration pneumonia, accident, or viral infection, respectively.[10] As a group, such deaths can be functionally described as 'epilepsy-related deaths', and they contribute a significant burden of total years of potential life lost.[5,11]

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is an ongoing global health emergency.[12] Neurological manifestations of COVID-19 are being increasingly recognised as a result of the direct neurotropic effects of the virus.[13,14] Worsening seizures during COVID-19 infection,[15,16] and failure to access emergency epilepsy treatment due to the increased burden of COVID-19 on healthcare services have been reported.[17] It is intuitive to hypothesise that the number of epilepsy-related deaths has increased during the COVID-19 pandemic. However, the evidence surrounding this is sparse and conflicting.[15,16,18-25] For example, a regional study in Spain reported increased fatality during hospitalisation in 21 PWE co-infected with COVID-19, after finding that five had died.[18] These findings have been disputed by other authors as generating unnecessary panic,[16] citing that they contradict with the results of two regional Chinese cohorts[21,22] and a regional care home study in England,[23] where there were no unexpected increases in epilepsy-related deaths in association with COVID-19 infection. This lack of an increase in epilepsy-related deaths has also been demonstrated in South Korea,[20] Italy,[19] and the US.[24] The outstanding research gaps mainly pertain to describing trends in epilepsy-related death during the COVID-19 pandemic in countries where this has not yet been reported, in order to see if the lack of an increasing number emerging in literature can be replicated. Furthermore, the burden of COVID-19 as an underlying cause of epilepsy-related death remains unclear.

To help address these gaps, we report the first national study to focus on epilepsy-related deaths during the COVID-19 pandemic in Scotland. We include an assessment of the burden of COVID-19 as an underlying cause of epilepsy-related death. The need to investigate Scotland is compounded by our knowledge that Scotland already has the lowest life expectancy of all western and central European countries (including England), meaning it is possible Scotland may not

follow the usual mortality trends.[26,27] We undertook a national population-based study to assess routinely collected mortality data in Scotland through the peak COVID-19 pandemic period of March–August of 2020 compared to the same periods in 2015–2019. We aimed to answer the following questions:

1) Did the number of epilepsy-related deaths in Scotland change during the COVID-19 pandemic period of 2020 compared to during the corresponding periods in 2015–2019?
2) What proportion of the epilepsy-related deaths in 2020 were found to also have COVID-19 listed as a cause A) anywhere in the cause of death record? and B) as the underlying cause of death in the record?
3) Was the proportion of deaths in which COVID-19 was listed anywhere or as the underlying cause different between people who experienced epilepsy-related deaths and people who experienced deaths unrelated to epilepsy?
4) Where was COVID-19 ranked, as an underlying cause of death, relative to all remaining underlying causes of death in people who experienced epilepsy-related deaths and in people who experienced deaths unrelated to epilepsy?

2 Methods

2.1 Study design, setting, and data sources

We undertook a nationwide, retrospective, cross-sectional study of routinely-collected mortality and demographic data pertaining to weeks 12 to 34 of the years 2015 to 2020 (i.e. mid-March to late August of each year) in Scotland. These are statutory data, routinely collated by the National Records of Scotland (NRS).[28-32] The free-text causes of death listed on death certificates are coded by NRS into their corresponding International Classification of Diseases Tenth Revision (ICD-10) codes.[33] There is a world-leading mortality review system in place in Scotland in which causes of death are routinely scrutinised for accuracy and amended, where necessary.[34] The amendments for the 2015–2018 periods included in the current study are finalised. Amendments to the causes for 2019–2020 are due for completion but remain of sufficient capacity and quality for scientific dissemination ahead of finalisation. These amendments are expected to relate to external causes of morbidity and mortality (ICD-10 codes V01–Y98) [personal communication with NRS], which are not the focus of the current study.

2.2 Case-ascertainment coding, participants, bias handling, and study size

Unsampled nationwide data were used to help reduce sampling bias and optimise study size.[35] ICD-10 codes G40–41 are commonly used to capture epilepsy within administrative healthcare datasets,[25,36] and they can do so with a high degree of accuracy, with positive predictive values (PPVs) and sensitivities >90%.[37,38] COVID-19 deaths are classified using ICD-10 codes U07.1–U07.2 as standard.[39-43] The diagnostic accuracy of these codes is still to be fully established, although there is emerging evidence to suggest high accuracy, with PPV >90% and 98–99% ranges for sensitivity and specificity.[44,45]

Eligible participants were deceased persons anywhere in Scotland, of any age, fulfilling any of the following criteria during the elected study periods:

A. **COVID-19-related death:** We defined COVID-19-related death using the same ICD-10 coding strategy as other authors of COVID-19-related death studies that use routine data,[41,42] which is also the same coding strategy used by NRS and the Office for National Statistics (ONS) to capture COVID-19-related death when reporting the UK's mandatory national mortality statistics,[39,40] and it is the coding strategy recommended by the World Health Organisation (WHO).[43] This strategy uses COVID-19 codes U07.1–07.2 listed as an underlying or contributory cause of death within death records to denote COVID-19-related death.[39,40,43] The U07.1 code describes when COVID-19 has been confirmed by laboratory testing irrespective of severity of clinical signs or symptoms.[39,40,43] The U07.2 code describes when COVID-19 is diagnosed clinically or epidemiologically but laboratory testing is inconclusive or not available.[39,40,43] Sensitivity analyses report little difference to study results between using U07.1 and using combined U07.1–07.2 codes anywhere on death certificates in studies of COVID-19-related death.[41] However, the latter strategy is likely to offer a more representative picture of a population as it is likely to include data from areas where resources may have been limited.

B. **Epilepsy-related death:** We defined epilepsy-related death using the same ICD-10 coding strategy as other authors of epilepsy-related death studies that use routine data,[46-48] which is also the same strategy used by NRS and the ONS to capture epilepsy-related death when reporting the UK's mandatory national mortality statistics,[49-51] and the same coding strategy used by the WHO to identify epilepsy in their mortality database.[52] This strategy uses codes G40–41 (epilepsy and/or status epilepticus) listed as an underlying or contributory cause of death within death records to denote epilepsy-related death.[25,36] Such a definition is consistent with national guidance that the presence of an epilepsy code/indicator anywhere in the cause of death record indicates that epilepsy (as for any disease) was thought by the certifying doctor to be either part of the sequence of events leading to death or else a factor contributing to the death.[10,28] Additional case-ascertainment benefit was drawn from the routine cause-of-death quality assurance processes in place to improve the accuracy of Scottish death certification and coding,[30,53] the robustness of which was highlighted recently.[34] These quality assurance processes helped reduce the likelihood of there being an underestimation in the number of epilepsy-related deaths captured by the study,[54,55] which can sometimes happen in studies using death certification. Post-mortem is expected to have occurred in around 20% of epilepsy-related deaths (with approximately 90% of SUDEP cases undergoing post-mortem).[54,56]

C. **Death unrelated to epilepsy:** These were captured when a person died with no mention of epilepsy (ICD-10 codes G40–41) as an underlying or contributory cause of death within their NRS death record. This captures any persons in Scotland who died of any cause other than epilepsy (i.e. the rest of Scotland's deceased population) – referred to

collectively as 'deaths unrelated to epilepsy' in the remaining text. This includes deceased PWE in whom their epilepsy was not felt to have caused death, as well as all other deceased persons in the general population without epilepsy.[10]

NRS provided frequencies for the underlying causes of death listed in the death records of all persons recruited. These were grouped into their respective ICD-10 chapters I–XX, with COVID-19 listed separately as its own ICD-10 chapter.[57,58] NRS also provided demographic data pertaining to age and sex.

2.3 Variables and statistical analysis

All analyses were carried out using R version 4.0.2 (2020-06-22).[59] Descriptive statistics were used to characterise the study population by mean age and by sex. 95% confidence intervals (CIs) for means and standard error (SE) were estimated using the Z Statistic. Missing data were not expected as NRS death registration is statutory, including where cause of death is unknown (where R95–R99 ICD-10 codes for 'ill-defined and unknown causes of mortality' are taken up).[58]

We assessed for change in the number of epilepsy-related deaths during the COVID-19 pandemic period of 2020 compared to previous periods in two ways. First, we estimated proportionate mortality for epilepsy-related death in each annual March–August period to see if this was different in 2020 compared to in 2015–2019. Proportionate mortality was calculated as the total number of epilepsy-related deaths in Scotland expressed as a percentage of all Scottish deaths. 95% CIs for the proportions were estimated using exact binomial tests.[60] Second, we used R statistical package tsoutliers (V0.6–8),[61] which is designed for the detection of outliers in a time series, to identify if the number of epilepsy-related deaths (overall, men and women) in March–August of 2020 were a statistical outlier compared to in 2015–2019. The package was run with an autoregressive integrated moving average (ARIMA) model.[61,62] Where outliers were present, a time series line graph of the original data was plotted alongside a series adjusted for the outlier effects. The outlier analysis was also undertaken for deaths unrelated to epilepsy in order to illustrate any background change in mortality during the COVID-19 pandemic period of 2020 compared to 2015–2019

To determine the proportion of epilepsy-related deaths found to also have COVID-19 listed as a cause anywhere in the cause of death record in 2020, deaths with both epilepsy and COVID-19 codes included in their cause of death record were taken as the numerator, with all epilepsy-related deaths set as the denominator. To determine the proportion of epilepsy-related deaths found to have COVID-19 listed only as the underlying cause, these deaths were taken as numerator, with all epilepsy-related deaths set as the denominator. These proportions were also calculated for deaths unrelated to epilepsy, allowing us to determine whether the proportion of deaths in which COVID-19 was listed anywhere or as the underlying cause was different between people who experienced epilepsy-related deaths versus people who experienced deaths unrelated to epilepsy. Exact binomial tests were used to determine the 95% CIs for these proportions.[60] Odds ratios (OR)

were also calculated for COVID-19 being listed anywhere or as the underlying cause in the epilepsy-related deaths versus the deaths unrelated to epilepsy, with 95% CIs.

In order to identify where COVID-19 ranked as an underlying cause of death relative to others, we estimated proportionate mortalities for all underlying causes of death for the epilepsy-related deaths population and for deaths unrelated to epilepsy. These were then able to be ranked in order from highest to lowest proportionate mortality in each group.

2.4 Approvals

Data were provided to us directly by NRS. The NHS Health Research Authority confirmed that this study of anonymised public data did not require ethical approval.[63]

3 Results

3.1 Population demographics

There were 141,701 deceased participants included across Scotland through March–August of 2015–2020 (figure 1). The mean age at which epilepsy-related death occurred ranged between 61–71 years (table 1). The mean age at which deaths unrelated to epilepsy occurred was older, ranging between 73–79 years. Women also tended to die at an older age than men, regardless of whether deaths were epilepsy-related or unrelated to epilepsy.

3.2 Change in the number of epilepsy-related deaths during COVID-19 compared to previously

Table 1 includes the proportionate mortality for epilepsy-related death in each March–August period of study, illustrating that epilepsy was recorded as underlying or contributing to 0.66–0.78% of all Scottish deaths in each period, with little change seen during the COVID-19 pandemic period of 2020.

There were 189 epilepsy-related deaths in Scotland through March–August of 2020 (100 in men, 89 in women). This was 25 more deaths (7 in men, 18 in women) compared to the mean corresponding number of epilepsy-related deaths in March–August of 2015–2019 (figure 2A). For women, this increase was classified as a statistical outlier, while for the total number and in men the increase could not be distinguished from the mean year-to-year variation expected (see tsoutliers results in appendix S1A–C). Ten of the 18 excess epilepsy-related deaths in women also had COVID-19 listed as one of the causes of death. COVID-19 was the underlying cause in nine out of the 10 women, and epilepsy was the underlying cause in the tenth woman. The remaining eight of 18 excess epilepsy-related deaths in women were unrelated to COVID-19.

There were 27,428 deaths unrelated to epilepsy in Scotland through March–August of 2020 (13,718 in men, 13,710 in women). These were more than the mean number of deaths unrelated to epilepsy during the corresponding periods of 2015–2019 irrespective of gender (i.e. the 2020 results were statistical outliers, see figure 2B, and tsoutliers results in appendix S1D–F). This was due to excess mortality from COVID-19. A second outlier is also noted in the results for deaths unrelated

to epilepsy in women, where the number of deaths in 2018 were fewer than might be expected from mean year-to-year variation.

3.3 Proportion of epilepsy-related deaths found to have COVID-19 listed anywhere or as the underlying cause of death in 2020

Twenty six out of the 189 epilepsy-related deaths in Scotland through March–August of 2020 also had COVID-19 listed as a cause of death anywhere in the death record (proportionate mortality 13.8%, 95% CI 9.2–19.5%, see in figure 1). In this same period, 4,202 out of the 27,428 deaths unrelated to epilepsy in Scotland also had COVID-19 listed as a cause of death anywhere in the death records (proportionate mortality 15.3%, 95% CI 14.9–15.8%). This equates to an OR of 0.88 (95% CI 0.58–1.34) for COVID-19 being listed anywhere in epilepsy-related deaths versus deaths unrelated to epilepsy. These results indicate that COVID-19-related deaths were unlikely to be much more common amongst those experiencing epilepsy-related deaths than in those experiencing deaths unrelated to epilepsy.

Twenty one out of the 189 epilepsy-related deaths in Scotland through March–August of 2020 had COVID-19 listed as the underlying cause of death in the death record (proportionate mortality 11.1%, 95% CI 7.0–16.5%, see in table 2 and figure 1). In the same period, 3,879 out of the 27,428 deaths unrelated to epilepsy in Scotland had COVID-19 listed as the underlying cause of death in the death record (proportionate mortality 14.1%, 95% CI 13.7–14.6%, see in table 3). This equates to an OR of 0.76 (95% CI 0.48–1.20) for COVID-19 being listed as the underlying cause in epilepsy-related deaths versus deaths unrelated to epilepsy. These results indicate that as an underlying cause of death, the burden of COVID-19 was similar between those experiencing epilepsy-related deaths and those experiencing deaths unrelated to epilepsy.

Where COVID-19 was ranked, as an underlying cause of death, relative to all remaining underlying causes

In March–August 2020, COVID-19 was one of the most common underlying causes of death both in those experiencing epilepsy-related deaths (where it was ranked fourth most common, see table 2), and in those experiencing deaths unrelated to epilepsy (where it was ranked third most common, see table 3). In the epilepsy-related deaths group, COVID-19 was as common an underlying cause of death as cancer.

4 Discussion

This is the first national study to focus on investigating epilepsy-related deaths during the COVID-19 pandemic in Scotland.[14-16,18,64] People of all ages were included from anywhere in Scotland. In response to the four research questions that were posed, we show that:

1) Although there was an increase in the absolute number of epilepsy-related deaths overall and in men during March–August of the COVID-19 pandemic in 2020, this increase could not be distinguished from mean year-to-year variation in epilepsy-related deaths across the corresponding periods in 2015–2019. However, in women, the 89 epilepsy-related

deaths observed in 2020 were an outlier compared to the average of 71 epilepsy-related deaths through 2015–2019, suggesting that the COVID-19 pandemic was associated with an increase in epilepsy-related mortality in women. The cause of death records indicate that some of the increased mortality was directly attributable to COVID-19 featuring as an additional (mainly underlying) cause of death alongside epilepsy in the chain of morbid events leading to death.

2) As many as 13.8% of epilepsy-related deaths also list COVID-19 as a cause of death, with 11.1% specifically listing it as the underlying cause of death.
3) The proportion of deaths in which COVID-19 is listed anywhere or as the underlying cause in the death record is similar between people who experienced epilepsy-related deaths and people who experienced deaths unrelated to epilepsy.
4) COVID-19 ranks as the fourth most common underlying cause of death in people experiencing an epilepsy-related death. In people experiencing a death unrelated to epilepsy, COVID-19 ranks as the third most common underlying cause of death. This suggests COVID-19 is a common underlying cause of death in both groups.

It may be somewhat reassuring that there were no major increases in epilepsy-related mortality overall during the peak of the COVID-19 pandemic in Scotland. However, the spike in epilepsy-related deaths seen in women requires further investigation. 56% of these deaths were directly COVID-19-related. General risk factors for death in relation to COVID-19 include older age, lower socio-economic status, Black, Asian and minority ethnic (BAME) background, and various clinical conditions including diabetes, obesity and cancer.[42,65] Whilst in the current study, epilepsy-related deaths occurred at an older age in women, we did not have information about these other potential confounders and were therefore unable to control for them. In the remaining 44% of excess epilepsy-related deaths in women during March–August of 2020, COVID-19 was not identified as an additional cause in the death records. Possible explanations for this include these being missed COVID-19 cases, or the deaths being indirectly related to COVID-19 through, for example, reduced access to emergency care,[17] increased stress exacerbating seizures,[66] or patients fearing hospital attendance.[67] This warrants further investigation as many of these factors are potentially modifiable. Our study makes incidental note of fewer female deaths unrelated epilepsy than expected in 2018, which is perhaps likely to have been part of a wider trend of fewer deaths seen in Scotland in the winter of 2018/19.[68]

Although PWE can die of causes unrelated to their epilepsy such as an assault or pulmonary embolism,[5] this study focuses on specifically ascertaining the burden of epilepsy-related deaths in PWE (i.e. those in whom epilepsy was identified by the certifying doctor as underlying or contributing to the death). This is based on our understanding that physicians and PWE are likely to wish to understand how COVID-19 may influence seizures and epilepsy.[66,69-72] This may help modify how seizures and epilepsy are managed during comorbid COVID-19 infection. Given that as many as 11% of all epilepsy-related deaths had COVID-19 listed as the underlying cause (a similar proportion to the number listing cancer as the

underlying cause), there is no doubting the negative impact of the virus on this group notwithstanding the mortality figures being similar in proportion to when deaths were unrelated to epilepsy. This negative impact is compounded further by the finding that epilepsy-related deaths tended to occur at a younger age than deaths unrelated to epilepsy regardless of COVID-19 status. This is consistent with our previous findings.[5]

Most chronic diseases are positively associated with increased risk of COVID-19-related death, including diabetes, asthma and other respiratory diseases, chronic heart disease, liver disease, stroke, dementia, and other neurological diseases.[42,73,74] However, taking into account our findings and those of other studies,[16,19-24] it may be that epilepsy is a unique chronic condition in that it does not appear to significantly contribute to the increased the risk of COVID-19-related death. However, caution is needed before such a conclusion can be fully drawn as more studies are still needed to replicate these findings elsewhere, particularly in countries where trends in epilepsy-related mortality during the COVID-19 pandemic have not yet been reported.

Our study is strengthened by the use of a nationwide administrative healthcare dataset, meaning that we analysed the available mortality data from an entire county's unsampled population, helping to improve generalisability of the study findings. The study also benefits from the use of epilepsy case-ascertainment codes that were validated previously,[36-38] along with a cause-of-death quality assurance processes set up to improve Scottish death certification through NRS.[34,55] We were able to report the differences between causes of death being reported anywhere in the cause-of-death sequence versus being the underlying cause. Being unable to do this was one of the limitations reported in a national Welsh study of epilepsy-related mortality during the COVID-19 pandemic.[25]

Our study is limited by lack of access to comorbidity and ethnicity data for the populations studied, which may have acted to confound the results.[42] The study was also undertaken at a peak time of the COVID-19 pandemic, prior to establishment of vaccination programs. Therefore, we are unable to comment on any confounding impact vaccination would have had on the study results. However, we would assume the overall conclusions would remain unchanged given the reductions in mortality related to COVID-19 following initiation of the vaccination programs. Finally, there remains a potential for inaccurate case-ascertainment in any study using ICD-10 coding to capture diseased participants, particularly where there are few coding diagnostic accuracy studies, as remains the case with COVID-19.[44,45]

In conclusion, this study finds little evidence to suggest there have been any major increases in deaths likely to have been epilepsy-related in Scotland overall and in men during the peak of the COVID-19 pandemic. However, there appears to have been a relatively large increase in women, requiring further investigation. COVID-19 is a common underlying cause of both epilepsy-related deaths and deaths unrelated to epilepsy, demonstrating similar proportionate mortality in both groups. Future work should aim to use additional sources, such as medical records, to identify the clinical spectrum and risk factors for epilepsy-related death during comorbid COVID-19 infection and identify if there are any indirect roles the

COVID-19 pandemic is having on epilepsy-related mortality. Studies differentiating trends in epilepsy-related mortality during the COVID-19 pandemic according to whether epilepsy was the underlying or a contributory cause will also be useful in future. These will require longer periods of assessment than in our study to ensure adequate sample sizes are captured in each group. Studies will also be needed to assess longer-term trends in epilepsy-related mortality following previous COVID-19 infection as we know that COVID-19 survivors experience a range of long-term effects, which are still being elucidated.[75,76] These could influence longer-term epilepsy-related morbidity and mortality outcomes.

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Disclosure of Conflicts of Interest

None of the authors has any conflict of interest to disclose.

Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. For the purpose of open access, the author has applied a Creative Commons Attribution (CC BY) licence to any Author Accepted Manuscript version arising from this submission.

Data Sharing Statement

All data analysed have been made available by the authors (https://datashare.is.ed.ac.uk/handle/10283/3790). This is an early, unedited extract taken directly from NRS. NRS subsequently changed all "not available" ICD-10 codes to U07.1–07.2 codes for COVID-19 once their coding platform was formatted to recognise the new codes.

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Figure legends

Figure 1 – Study flow diagram

Legend – Shows data flow from National Records of Scotland through the study for the corresponding study time periods of March–August of 2020 and the preceding periods in 2015 to 2019.

Abbreviations – ICD-10: International Classification of Diseases 10th revision; G40–41: codes for epilepsy–status epilepticus; U07.1–07.2: codes for COVID-19

Figure 2 – Time series of annual mortality in Scotland, March–August 2015–2020

Legend – Stars indicate unexpected high or low values (outliers) from the series predicted from the autoregressive integrated moving average (ARIMA) model (appendix S1).

Supporting Information Captions

Appendix S1 – Tsoutliers analysis results

Figure 1 - Study flow diagram

Click here to access/download;Figure;5) Figure 1 - Study flow diagram_v2.tif

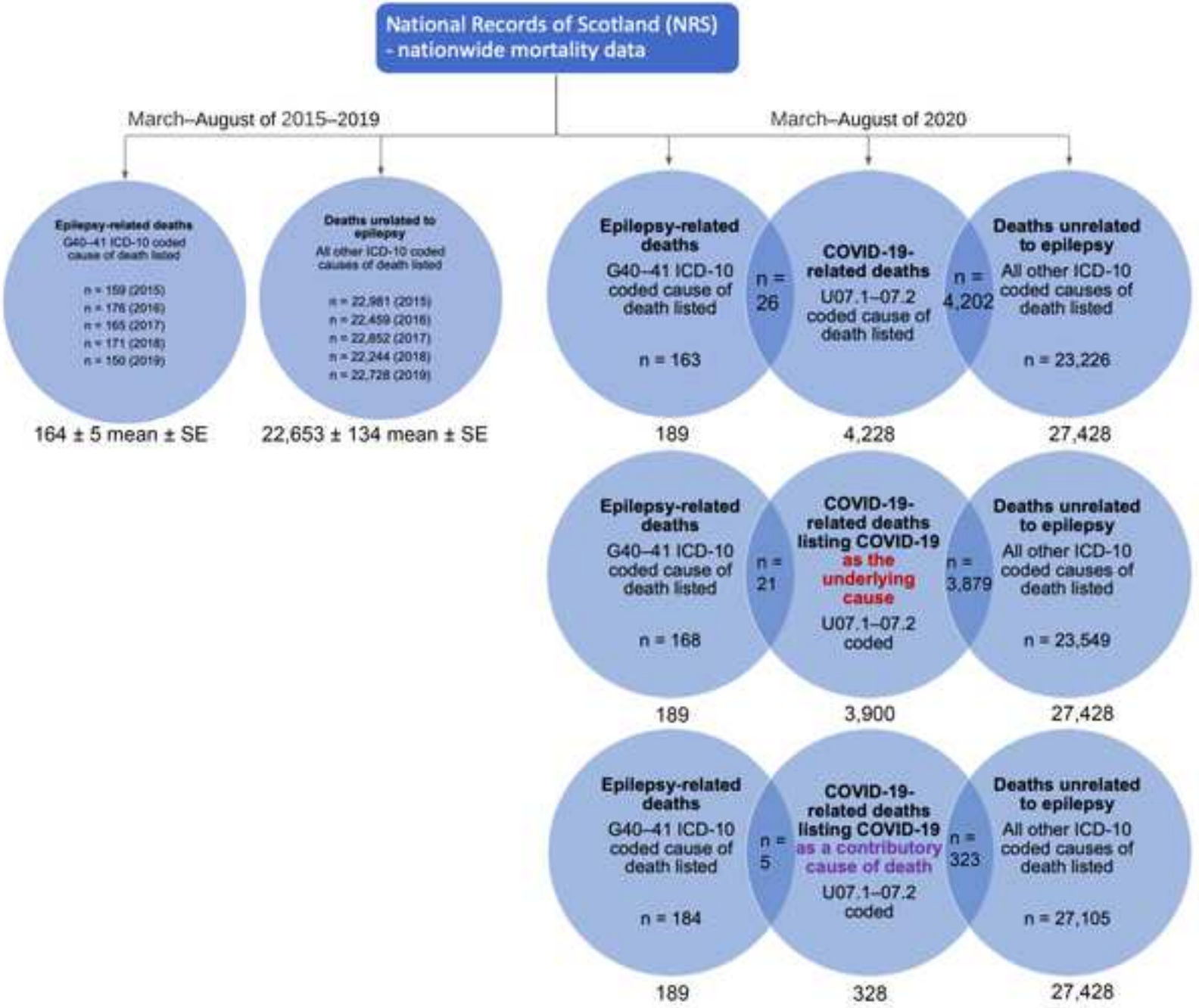

Figure 2 - Annual mortality time series

Click here to access/download;Figure;6) Figure 2 - Annual mortaity time series.tif

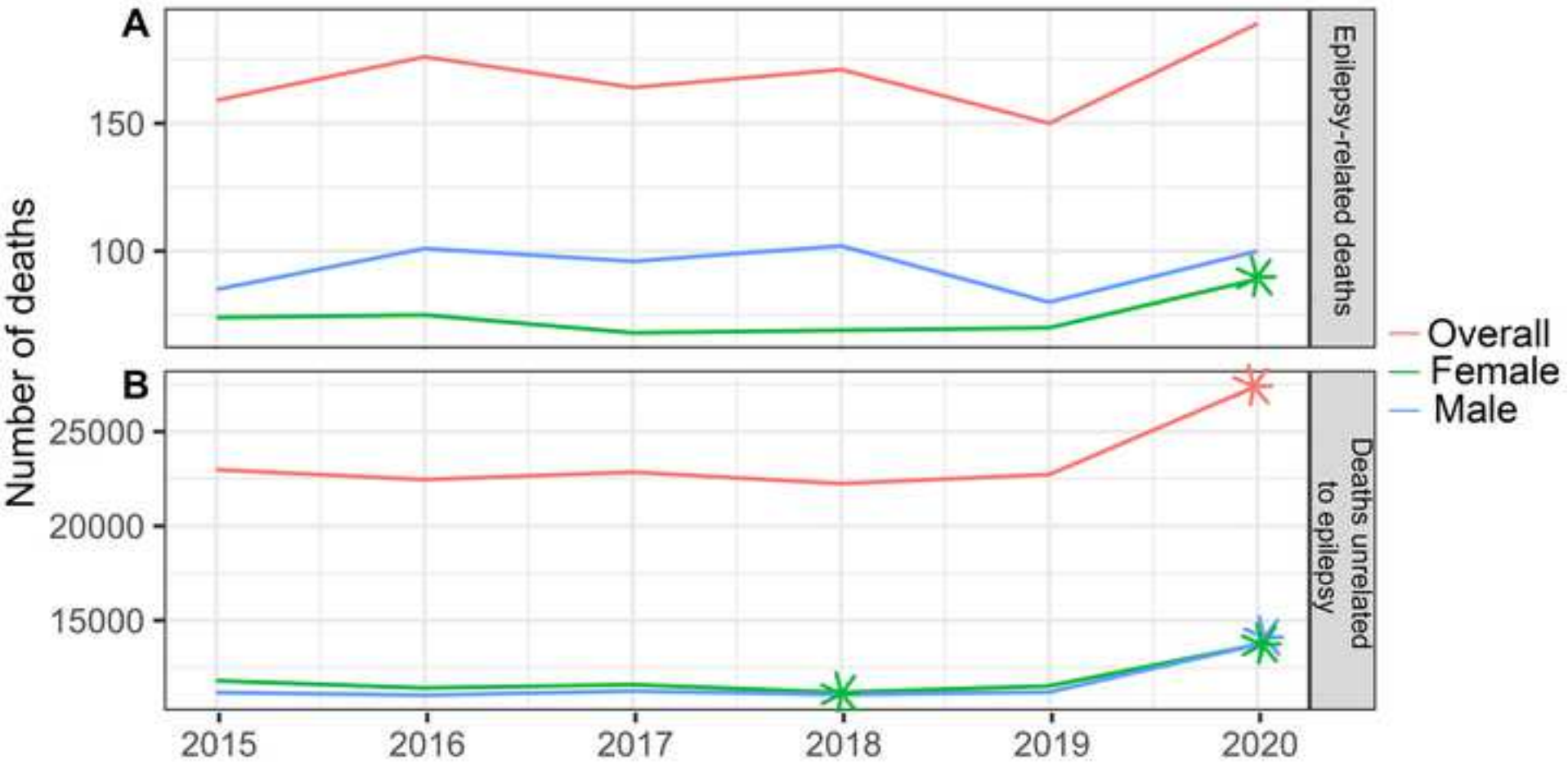

Table 1: Demographics of epilepsy-related deaths[1] and deaths unrelated to epilepsy in Scotland (March–August of 2015–2020)

Year	*Epilepsy-related deaths*	*Deaths unrelated to epilepsy*	*Total*	*Proportionate mortality for epilepsy-related deaths[2]*
2015	159 M = 85 (Mean age: 62, CI 58.1–66.5) F = 74 (Mean age: 66, CI 60.5–70.5)	22,981 M = 11,177 (Mean age: 73, CI 72.8–73.4) F = 11,804 (Mean age: 79, CI 78.6–79.1)	23,140	0.69% (CI 0.58–0.80%)
2016	176 M = 101 (Mean age: 62, CI 58.0–65.9) F = 75 (Mean age: 66, CI 61.1–70.8)	22,459 M = 11,042 (Mean age: 73, CI 72.3–72.9) F = 11,417 (Mean age: 78, CI 78.2–78.7)	22,635	0.78% (CI 0.67–0.90%)
2017	164 M = 96 (Mean age: 62, CI 58.3–65.5) F = 68 (Mean age: 69, CI 64.6–74.3)	22,852 M = 11,255 (Mean age: 73, CI 73.0–73.6) F = 11,597 (Mean age: 79, CI 78.3–78.8)	23,016	0.71% (CI 0.61–0.83%)
2018	171 M = 102 (Mean age: 66, CI 62.0–69.0) F = 69 (Mean age: 63, CI 57.6–67.6)	22,244 M = 11,064 (Mean age: 73, CI 72.6–73.2) F = 11,180 (Mean age: 78, CI 77.9–78.4)	22,415	0.76% (CI 0.65–0.89%)
2019	150 M = 80 (Mean age: 62, CI 57.3–65.9) F = 70 (Mean age: 69, CI 65.5–73.0)	22,728 M = 11,202 (Mean age: 73, CI 72.9–73.5) F = 11,526 (Mean age: 78, CI 78.1–78.6)	22,878	0.66% (CI 0.56–0.77%)
2020	189 M = 100 (Mean age: 69, CI 65.6–71.8) F = 89 (Mean age: 71, CI 68.2–74.7)	27,428 M = 13,718 (Mean age: 74 , CI 73.3–73.8) F = 13,710 (Mean age: 79, CI 79.1–79.6)	27,617	0.68% (CI 0.59–0.79%)

[1] *Epilepsy-related deaths, defined as ICD-10 codes G40–41 appearing in any position on the death certificate*

[2] *Number of epilepsy-related deaths ÷ total number of deaths from all causes*

Abbreviations: M – Male, F – Female, CI – 95% Confidence interval

Table 2: Frequency and proportionate mortality of epilepsy-related deaths[1] by underlying cause listed (March–August of 2015–2020)

Underlying cause of death, grouped by ICD-10 chapter (code range)	***Year (proportionate mortality, 95% CI)***					
	2015	**2016**	**2017**	**2018**	**2019**	**2020**
I. Infections (A00–B99)	2 (1.3%, 0.2–4.5%)	3 (1.7%, 0.4–4.9%)	1 (0.6%, 0.0–3.4%)	0 (0.0%, 0.0–2.1%)	2 (1.3%, 0.2–4.7%)	2 (1.1%, 0.1–3.8%)
II. Neoplasms (C00–D48)	17 (10.7%, 6.4–16.6%)	22 (12.5%, 8.0–18.3%)	15 (9.1%, 5.2–14.6%)	20 (11.7%, 7.3–17.5%)	21 (14.0%, 8.9–20.6%)	26 (13.8%, 9.2–19.5%)
III. Blood dis. (D50–D89)	1 (0.6%, 0.0–3.5%)	0 (0.0%, 0.0–2.1%)	0 (0.0%, 0.0–2.2%)	0 (0.0%, 0.0–2.1%)	1 (0.7%, 0.0–3.7%)	1 (0.5%, 0.0–2.9%)
IV. Endocrine/nutritional dis. (E00–E90)	3 (1.9%, 0.4–5.4%)	3 (1.7%, 0.4–4.9%)	5 (3.0%, 1.0–7.0%)	5 (2.9%, 1.0–6.7%)	2 (1.3%, 0.2–4.7%)	1 (0.5%, 0.0–2.9%)
V. Mental/behavioural dis. (F00–F99)	20 (12.6%, 7.9–18.8%)	9 (5.1%, 2.4–9.5%)	13 (7.9%, 4.3–13.2%)	7 (4.1%, 1.7–8.3%)	14 (9.3%, 5.2–15.2%)	11 (5.8%, 2.9–10.2%)
VI. Nervous system dis. (G00–G99)	64 (40.3%, 32.6–48.3%)	67 (38.1%, 30.9–45.7%)	68 (41.5%, 33.8–49.4%)	61 (35.7%, 28.5–43.3%)	55 (36.7%, 29.0–44.9%)	57 (30.2%, 23.7–37.2%)
IX. Circulatory dis. (I00–I99)	25 (15.7%, 10.4–22.3%)	49 (27.8%, 21.4–35.1%)	34 (20.7%, 14.8–27.7%)	43 (25.1%, 18.8–32.3%)	30 (20.0%, 13.9–27.3%)	37 (19.6%, 14.2–26.0%)
X. Lung dis. (J00–J99)	6 (3.8%, 1.4–8.0%)	7 (4.0%, 1.6–8.0%)	8 (4.9%, 2.1–9.4%)	4 (2.3%, 0.6–5.9%)	3 (2.0%, 0.4–5.7%)	5 (2.6%, 0.9–6.1%)
XI. Digestive dis. (K00–K93)	7 (4.4%, 1.8–8.9%)	3 (1.7%, 0.4–4.9%)	6 (3.7%, 1.4–7.8%)	9 (5.3%, 2.4–9.8%)	10 (6.7%, 3.2–11.9%)	8 (4.2%, 1.8–8.2%)
XII. Skin dis. (L00–L99)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.6%, 0.0–3.2%)	1 (0.7%, 0.0–3.7%)	2 (1.1%, 0.1–3.8%)
XIII. Musculoskeletal dis. (M00–M99)	2 (1.3%, 0.2–4.5%)	1 (0.6%, 0.0–3.1%)	0 (0.0%)	1 (0.6%, 0.0–3.2%)	1 (0.7%, 0.0–3.7%)	2 (1.1%, 0.1–3.8%)
XIV. Genitourinary dis. (N00–N99)	2 (1.3%, 0.2–4.5%)	2 (1.1%, 0.1–4.0%)	2 (1.2%, 0.1–4.3%)	0 (0.0%)	2 (1.3%, 0.2–4.7%)	4 (2.1%, 0.6–5.3%)
XV. Obstetric dis. (O00–O99)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%, 0.0–3.7%)	0 (0.0%)
XVII. Congenital dis. (Q00–Q99)	8 (5.0%, 2.2–9.7%)	2 (1.1%, 0.1–4.0%)	3 (1.8%, 0.4–5.3%)	6 (3.5%, 1.3–7.5%)	3 (2.0%, 0.4–5.7%)	6 (3.2%, 1.2–6.8%)
XVIII. Unclassified abnormality (R00–R99)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%, 0.0–2.9%)
XX. External causes (V01–Y98)	2 (1.3%, 0.2–4.5%)	8 (4.5%, 2.0–8.8%)	9 (5.5%, 2.5–10.2%)	14 (8.2%, 4.5–13.4%)	4 (2.7%, 0.7–6.7%)	5 (2.6%, 0.9–6.1%)
COVID-19 (U07.1–U07.2)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	21 (11.1%, 7.0–16.5%)
Total	**159**	**176**	**164**	**171**	**150**	**189**

[1] *Epilepsy-related deaths, defined as ICD-10 codes G40–41 appearing in any position on the death certificate*

Table 3: Frequency and proportionate mortality of deaths unrelated to epilepsy by underlying cause listed (March–August of 2015–2020)

Underlying cause of death, grouped by ICD-10 chapter (code range)	***Year (proportionate mortality, 95% CI)***					
	2015	**2016**	**2017**	**2018**	**2019**	**2020**
I. Infections (A00–B99)	297 (1.3%, 1.2–1.4%)	295 (1.3%, 1.2–1.5%)	271 (1.2%, 1.0–1.3%)	276 (1.2%, 1.1–1.4%)	250 (1.1%, 1.0–1.2%)	277 (1.0%, 0.9–1.1%)
II. Neoplasms (C00–D48)	6,823 (29.7%, 29.1–30.3%)	6,648 (29.6%, 29.0–30.2%)	6,694 (29.3%, 28.7–29.9%)	6,708 (30.2%, 29.6–30.8%)	6,899 (30.4%, 29.8–31.0%)	6,874 (25.1%, 24.5–25.6%)
III. Blood dis. (D50–D89)	52 (0.2%, 0.2–0.3%)	44 (0.2%, 0.1–0.3%)	40 (0.2%, 0.1–0.2%)	48 (0.2%, 0.2–0.3%)	60 (0.3%, 0.2–0.3%)	52 (0.2%, 0.1–0.2%)
IV. Endocrine/nutritional dis. (E00–E90)	426 (1.9%, 1.7–2.0%)	443 (2.0%, 1.8–2.2%)	557 (2.4%, 2.2–2.6%)	520 (2.3%, 2.1–2.5%)	529 (2.3%, 2.1–2.5%)	564 (2.1%, 1.9–2.2%)
V. Mental and behavioural disorders (F00–F99)	1,700 (7.4%, 7.1–7.7%)	1,513 (6.7%, 6.4–7.1%)	1,722 (7.5%, 7.2–7.9%)	1,571 (7.1%, 6.7–7.4%)	1,721 (7.6%, 7.2–7.9%)	1,722 (6.3%, 6.0–6.6%)
VI. Nervous system dis. (G00–G99)	1,146 (5.0%, 4.7–5.3%)	1,274 (5.7%, 5.4–6.0%)	1,438 (6.3%, 6.0–6.6%)	1,427 (6.4%, 6.1–6.7%)	1,420 (6.2%, 5.9–6.6%)	1,598 (5.8%, 5.6–6.1%)
VII. Eye dis. (H00-H59)	1 (0.0%, 0.0–0.0%)	2 (0.0%, 0.0–0.0%)	1 (0.0%, 0.0–0.0%)	0 (0.0%)	0 (0.0%, 0.0–0.0%)	2 (0.0%, 0.0–0.0%)
VIII. Ear dis. (H60-H95)	1 (0.0%, 0.0–0.0%)	5 (0.0%, 0.0–0.1%)	1 (0.0%, 0.0–0.0%)	0 (0.0%)	0 (0.0%, 0.0–0.0%)	2 (0.0%, 0.0–0.0%)
IX. Circulatory dis. (I00–I99)	6,340 (27.6%, 27.0–28.2%)	6,064 (27.0%, 26.4–27.6%)	5,980 (26.2%, 25.6–26.7%)	5,640 (25.4%, 24.8–25.9%)	5,790 (25.5%, 24.9–26.0%)	6,194 (22.6%, 22.1–23.1%)
X. Lung dis. (J00–J99)	2,805 (12.2%, 11.8–12.6%)	2,612 (11.6%, 11.2–12.1%)	2,557 (11.2%, 10.8–11.6%)	2,362 (10.6%, 10.2–11.0%)	2,319 (10.2%, 9.8–10.6%)	2,021 (7.4%, 7.1–7.7%)
XI. Digestive dis. (K00–K93)	1212 (5.3%, 5.0–5.6%)	1,231 (5.5%, 5.2–5.8%)	1,301 (5.7%, 5.4–6.0%)	1,310 (5.9%, 5.6–6.2%)	1,243 (5.5%, 5.2–5.8%)	1,353 (4.9%, 4.7–5.2%)
XII. Skin dis. (L00–L99)	72 (0.3%, 0.2–0.4%)	79 (0.4%, 0.3–0.4%)	71 (0.3%, 0.2–0.4%)	98 (0.4%, 0.4–0.5%)	92 (0.4%, 0.3–0.5%)	63 (0.2%, 0.2–0.3%)
XIII. Musculoskeletal dis. (M00–M99)	159 (0.7%, 0.6–0.8%)	150 (0.7%, 0.6–0.8%)	168 (0.7%, 0.6–0.9%)	165 (0.7%, 1.5–1.8%)	157 (0.7%, 0.6–0.8%)	163 (0.6%, 0.5–0.7%)
XIV. Genitourinary dis. (N00–N99)	494 (2.1%, 2.0–2.3%)	451 (2.0%, 1.8–2.2%)	383 (1.7%, 1.5–1.9%)	359 (1.6%, 0.6–0.9%)	370 (1.6%, 1.5–1.8%)	451 (1.6%, 1.5–1.8%)
XV. Obstetric dis. (O00–O99)	3 (0.0%, 0.0–0.0%)	3 (0.0%, 0.0–0.0%)	0 (0.0%)	2 (0.0%, 0.0–0.0%)	1 (0.0%, 0.0–0.0%)	4 (0.0%, 0.0–0.0%)
XVI. Perinatal dis. (P00-P96)	30 (0.1%, 0.1–0.2%)	50 (0.2%, 0.2–0.3%)	48 (0.2%, 0.2–0.3%)	35 (0.2%, 0.1–0.2%)	26 (0.1%, 0.1–0.2%)	33 (0.1%, 0.1–0.2%)
XVII. Congenital dis. (Q00–Q99)	59 (0.3%, 0.2–0.3%)	59 (0.3%, 0.2–0.3%)	67 (0.3%, 0.2–0.4%)	52 (0.2%, 0.2–0.3%)	43 (0.2%, 0.1–0.3%)	53 (0.2%, 0.1–0.3%)
XVIII. Unclassified abnormality (R00–R99)	199 (0.9%, 0.8–1.0%)	212 (0.9%, 0.8–1.1%)	240 (1.1%, 0.9–1.2%)	292 (1.3%, 1.2–1.5%)	337 (1.5%, 1.3–1.6%)	1,193 (4.3%, 4.1–4.6%)
XX. External causes (V01–Y98)	1,162 (5.1%, 4.8–5.3%)	1,324 (5.9%, 5.6–6.2%)	1,313 (5.7%, 5.4–6.1%)	1,379 (6.2%, 5.9–6.5%)	1,471 (6.5%, 6.2–6.8%)	930 (3.4%, 3.2–3.6%)
COVID-19 (U07.1–U07.2)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3,879 (14.1%, 13.7–14.6%)
Total	**22,981**	**22,459**	**22,852**	**22,244**	**22,728**	**27,428**

Disclosure of Conflicts of Interest

None of the authors has any conflict of interest to disclose.