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# Immune Checkpoint Inhibitor and Radiotherapy-Related Pneumonitis: An Informatics Approach to Determine Real-World Incidence, Severity, Management & Resource Implications

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Author contributions to the work are indicated with author initials as follows:

Guarantor of integrity of the entire study - RWL

Study concepts and design - SH, DC, MA, BS, KG, PM, NY, RWL

Literature research - SH

Data analysis - SH, DC, KG, BH, HK, RWL

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### *Abstract*

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Pneumonitis is a well-described, potentially life-threatening adverse effect of immune checkpoint inhibitors (ICI) and thoracic radiotherapy. It can require additional investigations, treatment, and interruption of cancer therapy. It is important for clinicians to have an awareness of its incidence and severity, however real-world data are lacking and do not always correlate with findings from clinical trials. Similarly, there is a dearth of information on cost impact of symptomatic pneumonitis. Informatics approaches are increasingly being applied to healthcare data for their ability to identify specific patient cohorts efficiently, at scale.

We developed a Structured Query Language (SQL)-based informatics algorithm which we applied to CT report text to identify cases of ICI and radiotherapy pneumonitis between 1/1/2015-31/12/2020. Further data on severity, investigations, medical management were also acquired from the electronic health record.

We identified 248 cases of pneumonitis attributable to ICI and/or radiotherapy, of which 139 were symptomatic with CTCAE severity grade 2 or more. The grade 2+ ICI pneumonitis incidence in our cohort is 5.43%, greater than the all-grade 1.3-2.7% incidence reported in the literature. Time to onset of ICI pneumonitis was also longer in our cohort (mean 4.5 months, range 4 days-21 months), compared to the median 2.7 months (range 9 days-19.2 months) described in the literature. The estimated average healthcare cost of symptomatic pneumonitis is £3932.33 per patient.

In this study we use an informatics approach to present new real-world data on the incidence, severity, management, and resource burden of ICI and radiotherapy pneumonitis. To our knowledge, this is the first study to look at real-world incidence and healthcare resource utilisation at the per-patient level in a UK cancer hospital. Improved management of pneumonitis may facilitate prompt continuation of cancer therapy, and improved outcomes for this not insubstantial cohort of patients.

### *Contribution to the field*

Pneumonitis is a well-described, potentially life-threatening adverse effect of immune checkpoint inhibitors (ICI) and thoracic radiotherapy. It can require additional investigations, treatment, and interruption of cancer treatment. It is important for clinicians to have an awareness of its incidence and severity, however real-world data are lacking and do not always correlate with findings from clinical trials. Similarly, there is a dearth of information on cost impact of symptomatic pneumonitis. Informatics approaches are increasingly being applied to healthcare data for their ability to identify specific patient cohorts efficiently, at scale. In this study, we draw upon a Structured Query Language (SQL)-based informatics approach to present new real-world data on the incidence, severity, management, and resource burden of ICI and radiotherapy pneumonitis. To our knowledge, this is the first study to look at real-world incidence and healthcare resource utilisation at the per-patient level in a UK cancer hospital. The latter is an important contribution, providing useful health economics data to inform future studies assessing cost-effectiveness of pneumonitis-related healthcare pathways. Additionally, we contribute evidence to the literature on the utility of informatics tools to extract real-world data from the electronic health record with reduced need for clinician time to manually collect such data.

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In review

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In review

## **Cancer-Immune Checkpoint Inhibitor and Radiotherapy-Related Pneumonitis: An Informatics Approach to Determine Real-World Incidence, Severity, Management & Resource Implications**

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20 **Health Economics,**

21

22 **Abstract**

23 Pneumonitis is a well-described, potentially life-threatening adverse effect of immune checkpoint  
24 inhibitors (ICI) and thoracic radiotherapy. It can require additional investigations, treatment, and  
25 interruption of cancer therapy. It is important for clinicians to have an awareness of its incidence and  
26 severity, however real-world data are lacking and do not always correlate with findings from clinical  
27 trials. Similarly, there is a dearth of information on cost impact of symptomatic pneumonitis.  
28 Informatics approaches are increasingly being applied to healthcare data for their ability to identify  
29 specific patient cohorts efficiently, at scale.

30 We developed a Structured Query Language (SQL)-based informatics algorithm which we applied to  
31 CT report text to identify cases of ICI and radiotherapy pneumonitis between 1/1/2015-31/12/2020.  
32 Further data on severity, investigations, medical management were also acquired from the electronic  
33 health record.

34 We identified 248 cases of pneumonitis attributable to ICI and/or radiotherapy, of which 139 were  
35 symptomatic with CTCAE severity grade 2 or more. The grade  $\geq 2+$  ICI pneumonitis incidence in our  
36 cohort is 5.43%, greater than the all-grade 1.3-2.7% incidence reported in the literature. Time to  
37 onset of ICI pneumonitis was also longer in our cohort (mean 4.5 months, range 4 days-21 months),  
38 compared to the median 2.7 months (range 9 days-19.2 months) described in the literature. The  
39 estimated average healthcare cost of symptomatic pneumonitis is £3932.33 per patient.

40 In this study we use an informatics approach to present new real-world data on the incidence,  
41 severity, management, and resource burden of ICI and radiotherapy pneumonitis. To our knowledge,  
42 this is the first study to look at real-world incidence and healthcare resource utilisation at the per-  
43 patient level in a UK cancer hospital. Improved management of pneumonitis may facilitate prompt  
44 continuation of cancer therapy, and improved outcomes for this not insubstantial cohort of patients.

45

## 46 **1 Introduction**

47 Pneumonitis is a well-described, potentially life-threatening and disabling adverse effect of several  
48 cancer therapies including immune checkpoint inhibitor (ICI) drugs and thoracic radiotherapy. The  
49 advent of ICI drugs, such as those targeting the Programmed Cell Death 1 receptor or its ligand  
50 (PD1/PD-L1), have transformed cancer treatment over the last decade. The numbers of patients  
51 receiving such drugs either alone or in combination therapy for various cancers continues to increase  
52 and an abundance of clinical trials elaborate upon further applications(1,2). Radiotherapy continues  
53 to be a major treatment modality for lung cancer and with an aging and increasingly comorbid  
54 population, the number of patients treated curatively with radiotherapy rather than surgery is likely to  
55 increase. As pneumonitis is observed in up to 5% of patients treated with ICI(3-5) and 40%  
56 following radiotherapy(6), it is likely to present a growing problem in cancer care. As pneumonitis  
57 can result in significant morbidity, preclusion of further treatment and even death(7), it is important  
58 for clinicians to have an awareness of its incidence and severity.

59 There is a lack of real-world incidence data in the literature, and that which exists does not always  
60 correlate with findings from clinical trials(8). Similarly, there is a dearth of information on health  
61 resource utilisation by patients with pneumonitis, which is an important element of economic  
62 evaluation studies seeking to explore whether new approaches to treatment are cost-effective.

63 Informatics approaches are increasingly being applied to healthcare data for their ability to identify  
64 specific patient cohorts at scale, more efficiently than traditional manual approaches. Here we use  
65 informatics tools to assist identification of cases of ICI and radiotherapy-pneumonitis and describe  
66 data on clinical management and impact of such cases in our specialist cancer centre from 2015-2020  
67 inclusive.

## 68 **2 Materials and Methods**

69 Using our integrated data warehouse and electronic health record (EHR) systems, we developed a  
70 Structured Query Language (SQL)-based informatics algorithm which we applied to CT Thorax  
71 report text to identify scans performed between 01/01/2015 and 31/12/2020 that contained key terms  
72 determined by radiology and respiratory expertise: “pneumonitis”, “pulmonary toxicity”, “lung  
73 toxicity”, “lung injury”, “interstitial lung disease” and “pneumonia”. This generated a list of 3,632  
74 CT reports. The report text, scan date and patient identifiers were extracted along with additional  
75 demographic and treatment details.

76 Such terms were typically located within the “request details” section of the report, where the  
77 requesting clinician had queried presence of “pneumonitis”, separately from the radiologist’s  
78 findings. In order to identify CT reports where the body of the report described findings relating to  
79 possible pneumonitis, further rules were applied to filter reports containing the terms “ground glass”,  
80 “treatment”, “drug”, “diffuse”, “infiltrates”, “radiotherapy”, “radiation” again guided by respiratory  
81 and radiology expertise. This filtered the number of reports down to 2,416.

82 Filters were also applied to structured treatment fields to identify only patients who had received any  
83 of the ICI drugs prescribed at our centre (Atezolizumab, Avelumab, Durvalumab, Ipilimumab,  
84 Nivolumab, Pembrolizumab) and/or to identify all patients that had received radiotherapy to the  
85 thorax/upper abdomen/neck/vertebrae/breast/chest wall prior to the date of the flagged CT report. A  
86 manual validation step was undertaken to eliminate any reports that did not suggest a possible  
87 pneumonitis. Reports from additional scans performed within 6 months of the identified scan for  
88 each patient were also eliminated, to limit the dataset to the earliest CT with reported pneumonitis.

89 The EHR of all patients with pneumonitis possibly attributable to ICI and/or RT was manually  
90 reviewed to identify the earliest date where potential pneumonitis symptoms (e.g. cough, dyspnoea)  
91 or clinical reference to pneumonitis began, and to ascertain severity of pneumonitis, which was  
92 inferred according to CTCAE v5.0 criteria (Supplementary Table 1). A case of pneumonitis was  
93 defined as a radiological report consistent with pneumonitis or treating clinician or multidisciplinary  
94 meeting consensus of pneumonitis based on the clinical picture at the time of presentation.  
95 [Pneumonitis was attributed to ICI if one of the above six drugs was administered within the](#)  
96 [preceeding three months, and considered radiotherapy-related if the patient was treated with radiation](#)  
97 [in the preceeding twelve months.](#) Fifty cases from the final cohort (20%) were randomly selected for  
98 independent review and scoring of CTCAE severity by a second clinician. The Krippendorff’s alpha  
99 measure of inter-observer correlation(9) was used to check concordance between both clinicians’  
100 interpretation of severity, calculated using the Natural Language ToolKit (NLTK) package in Python  
101 v 3.9.

102 Where symptoms were CTCAE grade 2 or more or treatment was withdrawn, additional data  
103 including investigations and medical management with steroids and/or antibiotics were collected  
104 manually from the EHR. Where a patient had more than one distinct episode of pneumonitis, this was  
105 recorded as a separate case. Further data were collected from the pharmacy database on the total  
106 number of patients treated with the above-mentioned ICI drugs (as mono- or combination-therapy)  
107 between 2015-2020 and for all patients deemed to have ICI or radiotherapy-related pneumonitis,  
108 clinical activity data was extracted algorithmically from the EHR including total number of  
109 consultant follow-up clinic attendances, CT thorax scan appointments and MDT discussions for the  
110 16-weeks after the date of pneumonitis diagnosis.

111

## 112 **3 Results**

### 113 **3.1 The Cohort**

114 We identified 450 CT reports indicating a pneumonitis in patients who had previously received ICI  
115 and/or radiotherapy, and thus which was possibly attributable to ICI/RT amongst other cause [Figure](#)  
116 [1](#)). In 248 cases [\(from 242 patients\)](#), the pneumonitis was attributed by the treating team as partially  
117 or completely due to ICI and/or radiotherapy-pneumonitis. In some cases, infection and other co-  
118 morbidities (e.g. pulmonary embolus or COPD) may have also contributed to the presentation as per

119 the clinical opinion of the treating team at the time; for example due to CT pulmonary angiogram  
120 results demonstrating the presence of both pulmonary emboli and features in keeping with  
121 pneumonitis, or raised inflammatory markers and pyrexia at presentation which responded to  
122 antibiotic therapy. One hundred and nine cases were asymptomatic (grade 1) and 139 were  
123 symptomatic with severity grade 2 or more. Results of symptomatic cases are presented below.

124 Table 1 shows the demographic and aetiology breakdown of symptomatic cases. Of the 139  
125 symptomatic cases, 61% of patients were male, the majority were performance status 0-1 and 20.14%  
126 were never-smokers. ICI accounted for 61.15% of cases with 7.19% of cases attributed to a  
127 combination of both ICI and radiotherapy.

128 Three quarters of cases were of grade 2 severity, 10.79% were grade 3 severity, 4 patients (2.88%)  
129 required intubation (grade 4) and 13 patients (9.35%) died (grade 5) (Figure 2). Of those that died,  
130 average time from first diagnosis of pneumonitis to death was 64 days (range 6-378). The number of  
131 cases increased year-on-year until 2020 after which there was a marked reduction (Figure 3). For the  
132 50 cases where a second clinician independently reviewed and scored CTCAE severity, the  
133 Krippendorff's alpha measure of inter-observer correlation demonstrated high concordance at 0.97.

134 One hundred and thirty-four symptomatic cases (96.4%) were treated with intravenous or oral  
135 steroids (Table 2). Two patients declined, 1 was treated with a steroid inhaler and in one grade 2 case,  
136 steroids were withheld due to concerns of possible COVID-19 and on-going tumour response to  
137 immunotherapy. A third of cases treated with oral steroids were given prophylactic co-trimoxazole at  
138 the time of steroid initiation, and this was mostly in cases where pneumonitis was described in the  
139 EHR to be ICI-related. Seventy-nine cases (57%) were treated with empirical antibiotics at initial  
140 presentation. Six cases (all ICI-pneumonitis) went on to receive another immunosuppressive therapy  
141 (Infliximab or Mycophenolate Mofetil).

142 Fifty-eight cases (42%) were referred for specialist respiratory management. The average time from  
143 first presentation with pneumonitis to being seen by the respiratory service was 34 days (range 0-  
144 215) with 40% and 55% of cases seen within 2 and 3 weeks of pneumonitis diagnosis respectively.  
145 Thirty-three cases (24%) went on to have a bronchoalveolar lavage (BAL). The average time from  
146 first presentation with pneumonitis to BAL was 35 days (range 1-149), with 58% of cases having  
147 BAL within 3 weeks. For those with grade 2 severity (n=20), average time to BAL was 41 days  
148 (range 1-149), and for those with grade 3-5 severity, was 24 days (range 1-91). Twelve cases (8.7%)  
149 had documented evidence of pulmonary function tests (PFTs) following diagnosis with pneumonitis.

150 Fifty-four cases were admitted to hospital with 10 requiring admission to critical care (CCU). The  
151 average length of hospital and CCU admission was 10.5 days (range 1-43) and 6.5 days (range 1-20)  
152 respectively.

### 153 **3.2 ICI related cases**

154 Of the 85 cases attributed to ICI, 32 (37.6%) had received pembrolizumab, 20 (23.5%) had received  
155 nivolumab and 11 (12.9%) combination therapy with ipilimumab and nivolumab (Supplementary  
156 Table 2). Thirteen (15.3%) were considered to have superadded infection. Three cases (3.5%) were  
157 due to a flare of underlying fibrosis or severe sarcoid-like reaction from ICI.

158 The mean time from starting ICI therapy to first presentation with pneumonitis was 4.5 months  
159 (range 4 days – 21 months). Forty-eight percent of cases presented within 3 months.

160 In 4 cases, patients had completed ICI therapy at the time of presenting with pneumonitis. Of the  
 161 remaining 81 cases, 28 (34.6%) were re-challenged with ICI therapy. The mean lost treatment time  
 162 between ICI being held and reintroduced was 73 days (range 11-275), however in some cases this  
 163 was due to other toxicities e.g. ICI-mediated colitis. Of the 28 cases that were re-challenged, 6  
 164 (21.4%) had recurrence of pneumonitis and had to stop treatment. In 6 cases (21.4%), patients had  
 165 disease progression within 2 cycles after resuming ICI and then stopped treatment. For these 6 cases,  
 166 the average treatment interruption was 74 days (range 29-150).

167 A total of 1565 patients were treated with ICI therapy in our centre between 2015-2020. Of these, we  
 168 identified 85 (5.43%) that developed symptomatic ICI-related pneumonitis (N.B. the 10 patients with  
 169 pneumonitis considered to be due to both RT and ICI therapy are not described here). Table 3  
 170 describes the proportion of pneumonitis cases by tumour-group, the highest of which were head and  
 171 neck and lung cancers. Figure 2 describes the number of ICI-pneumonitis cases by severity. Of the  
 172 total number of patients treated with ICI therapy, 62 (3.96%) were Grade 2, 11 (0.7%) were Grade 3,  
 173 4 (0.26%) were Grade 4 and 8 (0.51%) were Grade 5 respectively.

174

### 175 3.3 RT related cases

176 Forty-four cases were attributed to RT, of which 8 (18%) had received palliative dose-fractionation  
 177 schedules (ranging from 20 Gy in 5 fractions to 39 Gy in 13 fractions). The mean time from first  
 178 fraction of radiotherapy to first presentation with pneumonitis was 3.6 months (range 8 days-8  
 179 months). Nine cases (20.5%) were considered to have superadded infection. Of the total number  
 180 treated with RT, 35 (79.5%) were Grade 2, 4 (9.1%) were Grade 3 and 5 (11.4%) were Grade 5,  
 181 including 2 patients (4.5%) that had underlying fibrosis thought to be exacerbated by RT and both  
 182 patients died. The number of RT related cases were stable at approximately 10 per year between  
 183 2015-2020 (Figure 3).

184

### 185 3.4 Mixed RT and ICI related cases

186 Ten cases were in patients with a diagnosis of non-small cell lung cancer (NSCLC) who had received  
 187 both RT and ICI prior to presenting with pneumonitis. All 10 cases were of grade 2 severity. Of  
 188 these, 6 patients (60%) received Durvalumab. Five had prior treatment with concurrent  
 189 chemoradiotherapy (60-66Gy in 30-33 fractions) and one received Durvalumab after sequential  
 190 chemoradiotherapy 55Gy in 20 fractions). The remaining patients were treated with Pembrolizumab  
 191 (3 cases) or Atezolizumab (1 case) and palliative dose fractionation schedules (ranging from 20Gy in  
 192 5 fractions to 36Gy in 12 fractions). Three cases (30%) were considered to have superadded  
 193 infection.

194

### 195 3.5 Healthcare Resource Utilisation

196 The number of consultant follow-up clinic, CT thorax appointments and MDT discussions in the 16  
 197 weeks following pneumonitis diagnosis was compared between patients with grade 1 and grade 2-4  
 198 severity (Figure 4). The number of CT thorax scans and MDT discussions were broadly equal across  
 199 the groups however patients with grade 2-4 severity had approximately 50% more consultant follow-

200 up clinic appointments (unpaired t-test: P value <0.0001, difference in mean = 2.21, CI 1.34-3.07).  
201 Of the patients with grade 2-5 pneumonitis, 54 (39%) were admitted to hospital and 10 (7%) to CCU.  
202 The average duration of hospital admission was 10.5 days (range 1-43) per patient and CCU  
203 admission was 6.5 days (range 1-20) per patient.

204 In Table 4 we present the average use of resources associated with managing a symptomatic  
205 pneumonitis case. We recognise that resource utilisation will vary depending on severity and not  
206 every resource will be used for every case. Estimates for units used are based on data from this study  
207 (indicated with \*) and expert opinion (indicated with ^) on additional resources that gold-standard  
208 care is expected to include (PFTs and follow-up consultation for all cases requiring referral for  
209 specialist respiratory opinion). Units used have been weighted based on study data on the expected  
210 average use of resources by patients. For example, based on our data, only 4.3% of cases required  
211 other immunosuppressive therapy, only 41.7% a respiratory referral, and 23.7% bronchoscopy. Costs  
212 per unit were derived from the National Schedule of NHS costs 2019/2020 (NHS reference costs)(10)  
213 and British National Formulary (BNF)(11) and allow estimates on the average costs of healthcare per  
214 symptomatic pneumonitis case to be made (£3,932.33).

215 This is a conservative estimate as we have not included costs for empirical antibiotics, steroids, co-  
216 trimoxazole, pathology and microbiology services and have accounted only for CT thorax imaging,  
217 whereas in practice patients are likely to have had CT thorax, abdomen, and pelvis imaging.  
218 Furthermore, we have assumed patients that were referred for specialist respiratory input had only  
219 one initial and one follow-up appointment whereas in practice the number of follow-up appointments  
220 may have been higher.

221 To put this into context, applying the average cost per patient to the 139 symptomatic cases in our  
222 study who were treated at our centre between 2015-2020 leads to a total cost of £546,594.52. This is  
223 a cost of £91,099.09 per year.

224

## 225 4 Discussion

226 In this study we present new real-world data on the incidence, severity, management, and resource  
227 burden of cancer therapy pneumonitis. To our knowledge, this is the first study to look at real-world  
228 incidence and healthcare resource utilisation at the per-patient level in a UK cancer hospital. The  
229 latter is an important contribution, providing useful health economics data to inform future studies  
230 assessing cost-effectiveness of pneumonitis-related healthcare pathways. Additionally, we contribute  
231 evidence to the literature on the utility of informatics tools to extract real-world data from the EHR  
232 with reduced need for clinician time to manually collect such data.

233 The grade 2 or higher ICI-pneumonitis incidence in our cohort is 5.43%, which is greater than the all-  
234 grade 1.3-2.7% incidence reported in the literature(4,5) and higher than the all-grade pneumonitis  
235 from a large real-world series by Naidoo et al(3). For example, a meta-analysis of PD-1 inhibitor  
236 pneumonitis by Nishino et al demonstrated an all-grade incidence of 2.7%(5). Whilst our study also  
237 included PDL-1 and CTLA-4 related pneumonitis, making direct comparison difficult, this value is  
238 much lower than seen in our cohort. Similarly, grade 3-5 incidence in our cohort was 1.49%, higher  
239 than the 0.8% Grade 3-5 PD-1 pneumonitis rate described by Nishino et al(5). Time to onset of ICI-  
240 pneumonitis was also longer in our cohort (mean 4.5 months, range 4 days-21 months), compared to  
241 the median 2.7 months (range 9 days-19.2 months) described by Naidoo et al(3). In ninety-one  
242 patients receiving adjuvant Durvalumab following RT for NSCLC at our centre over the study

243 period, 6 (6.59%) developed pneumonitis, all of which were grade 2 severity. Our data demonstrates  
244 lower rates of grade 3-4 pneumonitis than the PACIFIC study, which reported all-grade and grade 3-  
245 4 pneumonitis rates of 12.6% and 1.9% respectively.

246 The incidence of pneumonitis in patients treated with combination ipilimumab and nivolumab was  
247 3.75%, lower compared to the incidence from single agent ICI. This contrasts findings in the  
248 literature which describe ICI-related pneumonitis most commonly occurring in patients receiving  
249 combination treatment(3,8). A higher incidence of ICI-pneumonitis is reported in patients with non-  
250 small cell lung cancer and with squamous cancers(5,8). This is reflected in our cohort which  
251 demonstrated highest incidence in head and neck (11.48%) and lung (9.01%) tumour groups.

252 Twenty-eight patients who developed ICI-pneumonitis at our centre had ICI re-introduced on  
253 resolution of symptoms. Six (21.4%) had disease progression within 2 cycles of restarting treatment.  
254 The average interruption in treatment was 74 days (range 29-150) and it is possible that this  
255 interruption may have led to loss of immunomodulation and control of cancer.

256 Almost 20% of RT pneumonitis cases had received palliative dose-fractionation schedules. Whilst  
257 there may be confounding factors including larger irradiated volume and possibly frailer patients with  
258 heart-failure or disease progression contributing to the presentation, this may be an important factor  
259 when considering quality of life in deciding which patients would benefit from palliative treatment.  
260 Mean time to onset of RT pneumonitis in our cohort fit with that described in the literature(6).

261 Of note, the number of cases of ICI-pneumonitis increased year on year from 2015-19 but then  
262 reduced in 2020. This is inconsistent with the number of patients treated with ICI overall at our  
263 centre which continued to increase in 2020 (Supplementary Table 3). The explanation for this is  
264 likely multifactorial, however one possibility may be the impact of the COVID-19 pandemic, due to  
265 increased local hospital care or misdiagnosis of ICI-pneumonitis as COVID-19 due to overlapping  
266 clinical and radiological features(12–14), particularly if patients presented to departments less  
267 familiar with the diagnosis and management of ICI-toxicity. It is possible that growing understanding  
268 of ICI-pneumonitis results in earlier identification and optimal management. In particular, there is a  
269 need to identify patients at risk of developing grade  $\geq 3+$  pneumonitis as early as possible and this is  
270 an area where artificial intelligence and machine learning predictive models may provide significant  
271 clinical utility.

272 Such considerations support the need for wider education on cancer therapy toxicity including  
273 differential diagnoses and the potential role of acute oncology, respiratory and microbiology services  
274 in recognising this. Continued surveillance and analysis of pneumonitis incidence will be important  
275 and may be benefited by a national pneumonitis registry. Here we have provided an indicative list of  
276 resource use for symptomatic pneumonitis based on a combination of study data and expert opinion,  
277 and an indicative, conservative estimate of healthcare cost per patient. Whilst we do not have data on  
278 the UK-wide incidence for ICI or radiotherapy-pneumonitis to provide estimates at population-level,  
279 the economic impact at our centre is estimated at over £90,000 per year. Earlier detection and  
280 improved management of pneumonitis could potentially reduce such costs. Future research on the  
281 health economic aspects of ICI or radiotherapy-pneumonitis will allow us to estimate more precisely  
282 the economic burden on the NHS.

283 Our study has several limitations. Due to its retrospective nature, the data presented relies on EHR  
284 documentation which may contain inaccuracies, especially when referring to investigations  
285 performed outside our centre such as BAL and PFTs. An example was concurrent administration of

286 prophylactic co-trimoxazole with steroids which appeared variable. It is difficult to ascertain from  
287 retrospective EHR data the reasons for this. One explanation is that steroids were started on the  
288 assumption that symptoms would improve and when they didn't, the course was extended and  
289 prophylactic co-trimoxazole was introduced. Improved education on recording key clinical decisions  
290 in medical notes is often encouraged as a gold-standard of documentation. Considering informatics  
291 requirements with respect to such principles highlights a need for more structured data fields that in-  
292 turn could integrate with drug toxicity analytics and decision support systems – e.g. the recording of  
293 a steroid prescription in the EHR then presents the clinician with a data field asking if prophylactic  
294 co-trimoxazole, proton-pump inhibitor or bisphosphonate is indicated, thus providing additional data  
295 at the same time as standardising care.

296 A further limitation of informatics approaches is that the identification of cases is dependent on  
297 defining comprehensive search terms. Missed cases, [or indeed those investigated with chest x-ray](#)  
298 [rather than CT](#) would lead to underestimates of the incidence of pneumonitis in this cohort or favour  
299 identification of milder cases that are defined with radiological reports but not actioned by clinical  
300 teams as significant. Informatics approaches do however tend to be more comprehensive than manual  
301 searches for cases given their broad vision of the entire EHR dataset and are therefore a valuable  
302 route to define descriptive statistics of the broader cohort identified, which may improve upon more  
303 traditional methods of audit and research and can be scaled up to larger data sets, with less person-  
304 hour requirements.

305 This is a single-centre study and therefore may not reflect variation in practice across centres, but our  
306 experience is that such tools can be readily applied in other centres and are thus well placed to drive  
307 acquisition of much larger datasets, in collaboration with others, where this can facilitate greater  
308 understanding and allow comparison between centres or creation of a lung toxicity registry.

309 Overall, the use of ICI has increased over the last 6 years and with that as has the incidence of ICI-  
310 related pneumonitis. Our data suggests the incidence of ICI-pneumonitis is higher, and time to onset  
311 is longer compared to the literature. The number of patients receiving ICI therapy and subsequently  
312 the number presenting with possible ICI-pneumonitis is likely to continue to increase, placing  
313 demand on acute oncology and specialist respiratory services, and potentially hospital and CCU  
314 admissions. It is imperative that funding and resource provision is made available to support  
315 increasing demand on such pathways and to ensure adequate provision of acute oncology, respiratory  
316 and microbiology services - for example, rapid access to BAL to aid diagnosis, and PFTs to define  
317 severity. Improved management of pneumonitis may facilitate prompt continuation of cancer therapy,  
318 and improved outcomes for this not insubstantial proportion of our ICI or thoracic radiotherapy  
319 treated patients.

320

## 321 **5 Conflict of Interest**

322 Sumeet Hindocha is funded by the UKRI CDT in AI for Healthcare <http://ai4health.io> (Grant No.  
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337 Mary O'Brien reports advisory work for MSD, BI, Abbot, Pierre Fabre and Roche outside the  
338 submitted work.

339 Sanjay Popat reports personal fees from BMS, Roche, Takeda, AstraZeneca, Pfizer, MSD, EMD  
340 Serono, Guardant Health, Abbvie, Boehringer Ingelheim, OncLive, Medscape, Incyte, Paradox  
341 Pharmaceuticals, Eli Lilly, outside the submitted work.

342 Richard Lee is funded by the Royal Marsden Cancer Charity with grant funding from Cancer  
343 Research UK, Innovate UK (co-funded with Roche and Optellum), and RM Partners outside of the  
344 submitted work.

## 345 **6 Author Contributions**

346 Author contributions to the work are indicated with author initials as follows:

347 Guarantor of integrity of the entire study – RWL

348 Study concepts and design – SH, DC, MA, BS, KG, PM, NY, RWL

349 Literature research – SH

350 Data analysis – SH, DC, KG, BH, HK, RWL

351 Manuscript preparation – SH

352 Manuscript editing – SH, KG, BH, MA, HK, BS, PM, WC, MD, NY, JB, AM, IL, FM, MO, SP,  
353 RWL

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355 No funding was specifically required for this work.

## 356 **8 Acknowledgments**

357 Nil applicable.

## 358 **1 Data Availability Statement**

359 The dataset utilized in this work contains personal patient identifiable data and is thus not publicly  
 360 available, in keeping with the organisation's Data Protection Policy.

361

## 362 2 Figure Captions

363 Figure 1: Flow of data to identify cases for inclusion. RT = radiotherapy.

364 Figure 2: Symptomatic pneumonitis severity by cause.

365 Figure 3: Number of symptomatic cases per year by cause.

366 Figure 4: The mean number of cases requiring CT thorax scan, MDT discussion and consultant  
 367 follow-up clinic appointment in the 16 weeks following pneumonitis diagnosis, by severity.

## 368 3 Tables

369 Table 1: Symptomatic (grade  $\geq 2+$ ) pneumonitis demographics and aetiology.

Demographics and Causes	Number
Age	Average 66, Range: 27-87
Gender	
Male	85 (61%)
Female	54 (39%)
Performance Status	
0	20 (14.4%)
1	89 (64%)
2	21 (15.1%)
3	5 (3.6%)
No Data	4 (2.9%)
Smoking Status	
Never	28 (20.14%)
Ex	82 (58.99%)
Current	11 (7.91%)
No Data	18 (12.94%)

Aetiology	
Radiotherapy	44 (31.65%)
ICI	85 (61.15%)
Radiotherapy and ICI combined	10 (7.19%)

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Table 2: Medical treatment, investigation, and management for symptomatic pneumonitis.

Medical treatment	All Cases [n=139]	ICI Cases [n=85]	RT Cases [n=44]	RT and ICI Cases [n=10]
Empirical antibiotics	79 (56.8%)	49 (57.6%)	25 (56.8%)	5 (50%)
Steroids (oral or intravenous)	134 (96.4%)	84 (98.8%)	40 (90.9%)	10 (100%)
Prophylactic co-trimoxazole at initiation of oral steroids	41 (29.5%)	37 (43.5%)	1 (2.3%)	3 (30%)
Other immunosuppressive agent	6 (4.3%)	6 (7.1%)	0	0
Investigation and management				
Referral to Respiratory Specialist	58 (41.7%)	40 (47%)	15 (34%)	3 (30%)
Average time [and range] from pneumonitis diagnosis to respiratory review (days)	34 [0-215]	30 [0-135]	35 [2-128]	75 [2-215]
Broncho-alveolar lavage	33 (23.7%)	28 (32.9%)	5 (11.4%)	0
Average time [and range] from pneumonitis diagnosis to BAL (days)	35 [1-149]	32 [1-149]	52 [6-128]	NA
Pulmonary function test (PFT) following diagnosis of pneumonitis	12 (8.6%)	9 (10.6%)	3 (6.8%)	0
Admission to hospital	54 (38.8%)	39 (45.9%)	13 (29.5%)	2 (20%)
Average duration [and range] of hospital admission (days)	10.5 [1-43]	10 [1-43]	15 [1-39]	2 [1-2]
Admission to CCU/ITU	10 (7.2%)	7 (8.2%)	3 (6.8%)	0
Average duration [and range] of CCU/ITU admission (days)	6.5 [1-20]	7 [1-20]	7 [3-11]	NA

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Table 3: The number of patients receiving ICI therapy and developing symptomatic ICI-related pneumonitis between 2015-2020.

Tumour Group	Patients receiving ICI therapy [n=1565]	G <sub>≥2+</sub> ICI pneumonitis cases [n=85]	Proportion of pneumonitis cases by tumour group (%)
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Breast	35	-	-
GI	144	10	6.9
Gynae	47	-	-
H&N	61	7	11.5
Lung	433	39	9.0
Lymphoma	25	-	-
Sarcoma	29	2	6.9
Skin	522	18	3.4
Urology	269	9	3.3

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377 Table 4: The estimated average per-patient cost of symptomatic pneumonitis based on NHS reference  
378 and BNF unit costs. FU – follow up, CL- consultant led, OPROC-outpatient procedures, IMAG –  
379 Diagnostic Imaging, CMDT-Cancer multidisciplinary team meetings, CC-Critical Care, NES- Non-  
380 elective short stay. Resource utilisation units have been based on data extracted from healthcare  
381 records (\*) or expert opinion (^) and have been weighted based on study data on the expected  
382 average use of resources. Infliximab is used here as an example of “other immunosuppressive agent”.  
383 The cost per unit is based on a course of 5mg/kg twice daily for 5 days. For a 70kg patient this is  
384 3500mg. The BNF cost is £377 for 100mg.

Resource	Units used (weighted)	Cost per unit (£)	Currency or service code	Total Estimated Cost (£)
Initial respiratory appointment (CL)*	0.417	198.52	WF01B	82.78
FU respiratory appointment (CL) ^	0.417	209.12	WF02A	87.20
Bronchoscopy*	0.237	703.86	DZ69A (OPROC)	166.81
PFT ^	0.417	156.75	DZ52Z (OPROC)	65.36
CT Thorax scan*	1	68.92	RD21A (IMAG, outpatient)	68.92
MDT discussion*	1	127.45	Average of CMDT-B, -C, -LG, -OTH, -SPU, -SPG	127.45
FU Oncology appointment (CL) *	2	200.38	WF01A	400.76
Hospital admission (nights) *	10.5 x 0.07	473.97	DZ19M (NES)	1,940.91

CCU admission (nights)*	6.5 x0.39	933.51	CCU03, XC06Z (CC)	424.75
Other immunosuppressive agent*	0.043	13,195	BNF	567.39
<b>Total average cost per patient</b>				<b>£3,932.33</b>

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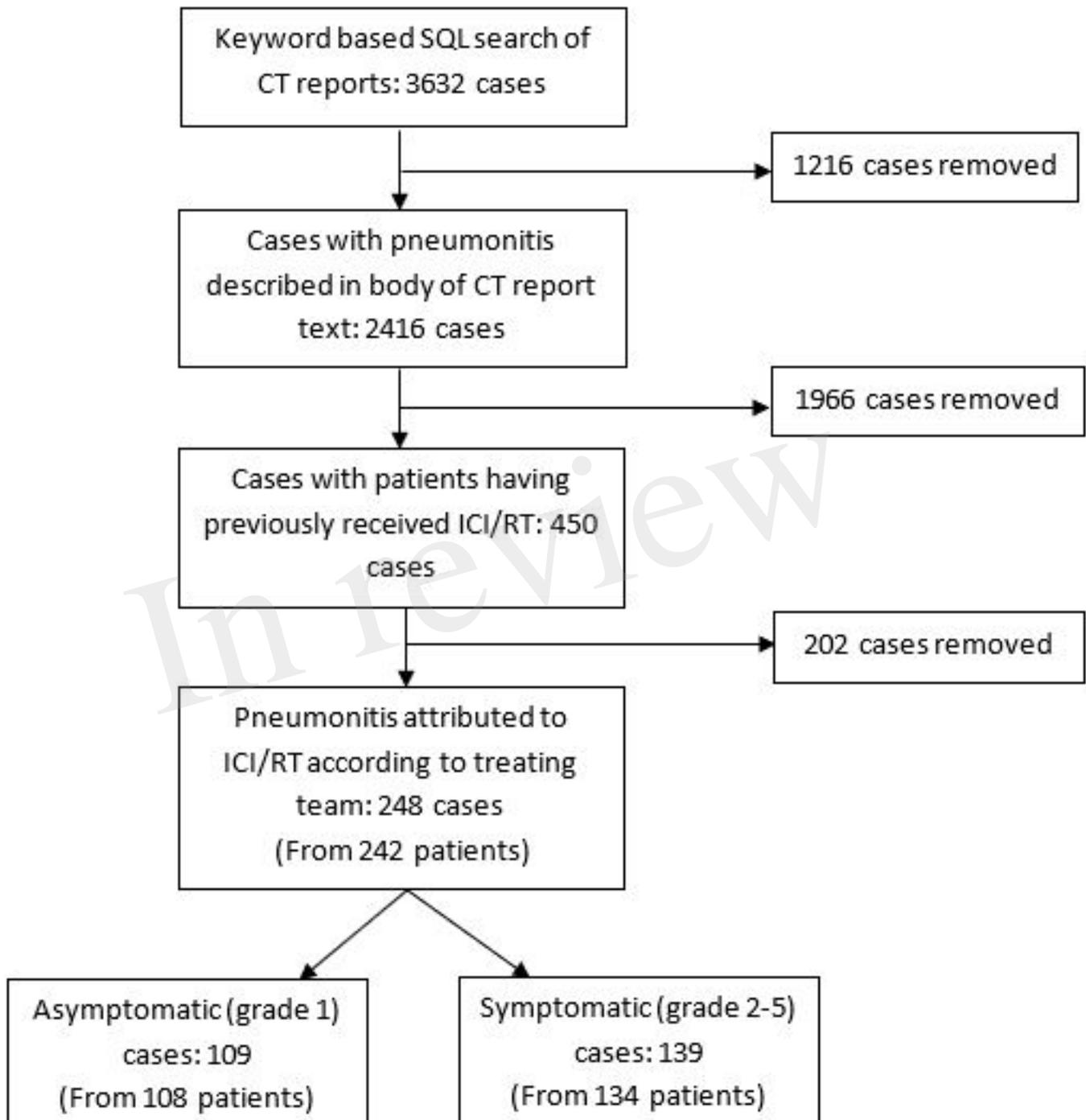
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**Figure 1. Flow of data to identify cases for inclusion. RT = radiotherapy.**

Figure 2.JPEG

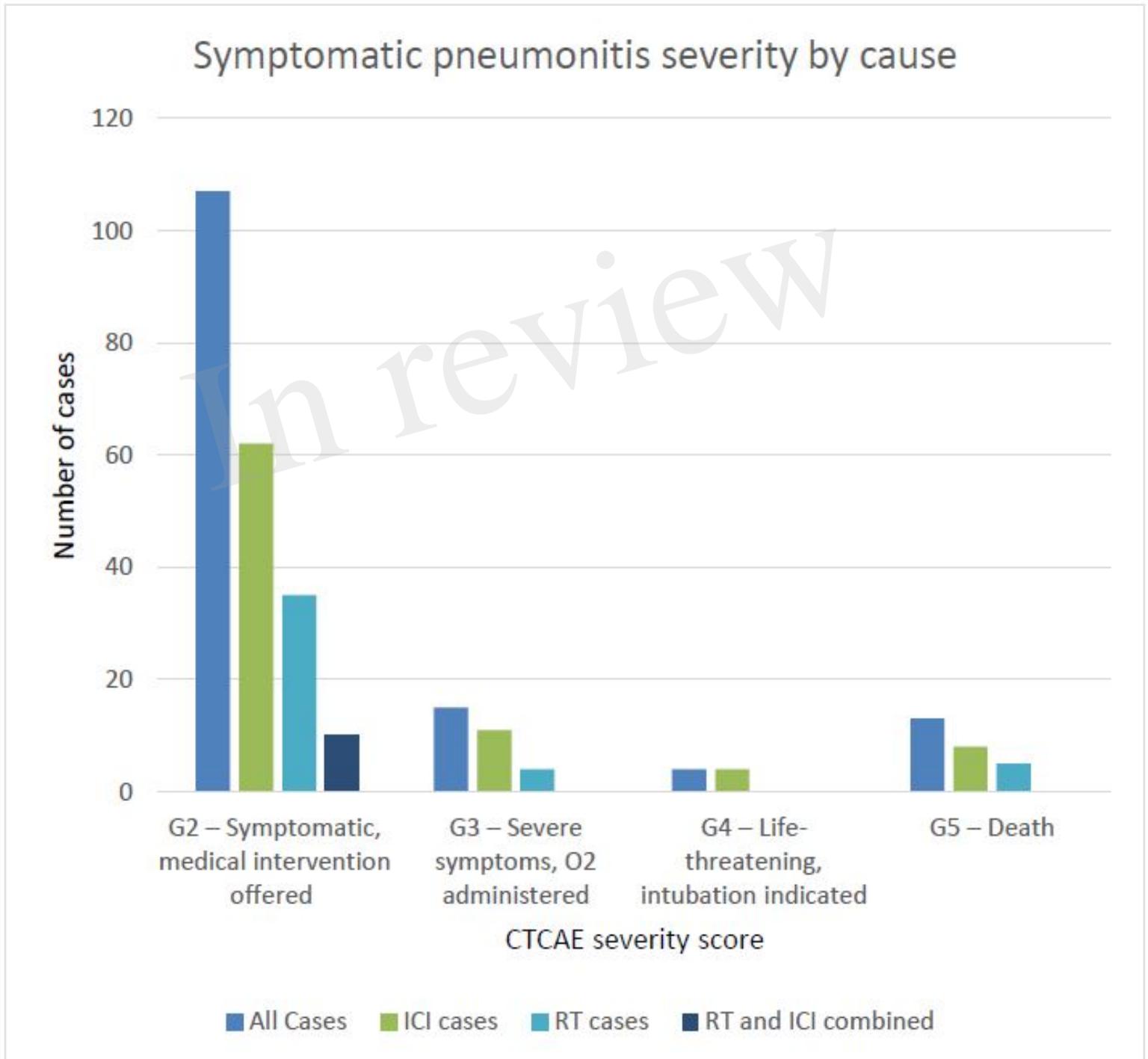


Figure 3.JPEG

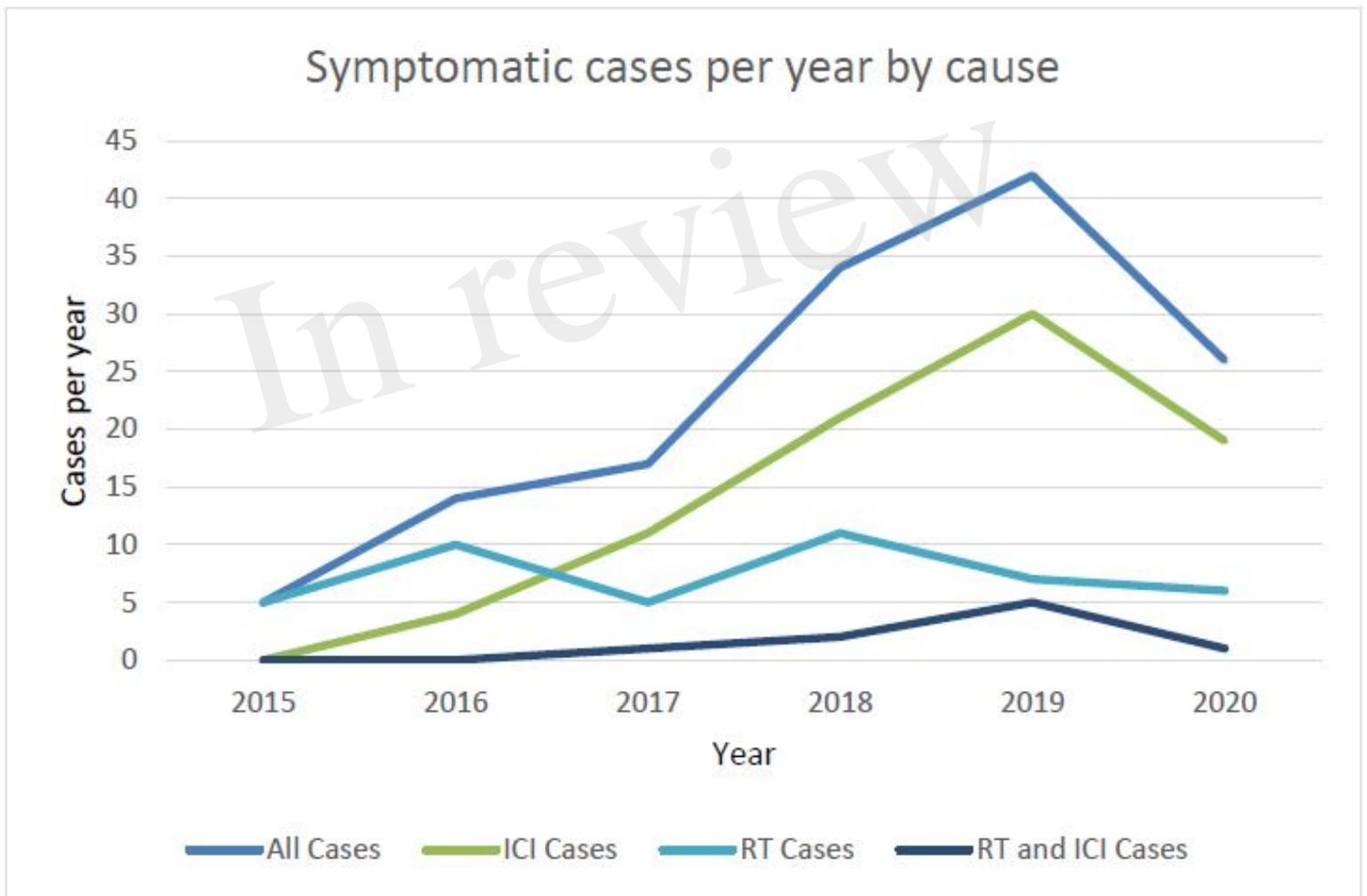


Figure 4.JPEG

### Differences in follow-up activity by severity

