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An appraisal of the frequency and severity of noninfectious manifestations in primary immunodeficiencies: A study of a national retrospective cohort of 1375 patients over 10 years

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1 **An appraisal of the frequency and severity of non-infectious manifestations in primary**
2 **immunodeficiencies. A study of a national retrospective cohort of 1375 patients over 10 years**
3
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57

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61

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73 **Abbreviations (by alphabetical order)**

74 AT: Ataxia-Telangiectasia

75 CGD: Chronic granulomatous disease

76 CID: Combined Immunodeficiency

77 CVID: Common Variable Immunodeficiency

78 ESID: European Society for Immunodeficiencies

79 HIES: Hyper-IgE syndrome

80 HLH: Hemophagocytic lymphohistiocytosis

81 HSCT: Hematopoietic stem cell transplantation

82 IgRT: Immunoglobulin replacement therapy

83 PID: Primary Immunodeficiencies

84 WAS: Wiskott-Aldrich syndrome

85

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93

94 **Capsule summary (35 words)**

95 Non-infectious manifestations, i.e. allergy, autoimmunity/inflammation, lymphoproliferation
96 and malignancies are frequent and severe manifestations in various PID categories across all
97 age groups, emphasizing the importance of care by a multidisciplinary team of healthcare
98 professionals for every single patient.

99

100 **Clinical Implications (29 words)**

101 Non-infectious manifestations, i.e. allergy, autoimmunity/inflammation, lymphoproliferation
102 and malignancies in PID are more frequent than previously thought and should be assessed
103 carefully throughout the life course of all PID patients.

104

105

106 **Abstract**

107 **Background:** Non-infectious manifestations, i.e. allergy, autoimmunity/inflammation,
108 lymphoproliferation and malignancies are known to be observed in many primary
109 immunodeficiency diseases (PID) and to participate to their prognosis.

110 **Objective:** In order to have a global view on their occurrence, we retrieved data from a
111 retrospective cohort of 1375 patients included in the French national registry of PID (CEREDIH)
112 for whom we had a 10-year follow-up since inclusion in the registry.

113 **Methods:** These patients were followed for 10 years (2009-2018) by specialized centers in
114 University Hospitals. This study shows that 20.1% of patients without prior curative therapy
115 (n=1163) developed at least one manifestation (event) encompassing 277 events.

116 **Results:** Autoimmune/inflammatory events (n=138) and malignancies (n=85) affected all age
117 classes and virtually all PID diagnostic groups. They were associated with a risk of death that
118 occurred in 14.2% of them (n=195), being found as causal in 43% of cases. Malignancies (OR:
119 5.62 [3.66 – 8.62]) and autoimmunity (OR: 1.9 [1.27 – 2.84]) were clearly identified as risk
120 factors for lethality. Patients who underwent curative therapy (i.e. mostly allogeneic
121 hematopoietic stem cell transplantation, a few cases of gene therapy or thymic
122 transplantation) prior to the 10-year study period (n=212) had comparatively reduced but still
123 detectable clinical manifestations (n=16) leading to death in 9.4% of them.

124 **Conclusion:** This study points to the frequency and severity of non-infectious manifestations
125 in various PID groups across all age groups. These results warrant further prospective analysis
126 to better assess their consequences and to adapt therapy, notably indication of curative
127 therapy.

128

129 **Introduction**

130 Primary immunodeficiencies (PID) represent a group of over 430 inherited diseases, with an
131 estimated incidence of 1:3000 per year (1,2). Most are life-threatening diseases because these
132 many conditions cause vulnerability to severe and recurrent infections but also because they
133 are associated with immunopathology and cancer (3,4). This is justifying the efforts to collect
134 as much as possible information on the mechanisms and pathophysiology of these various
135 PIDs. Dedicated clinical centers caring from such complex cases have accordingly been
136 developed all over the world.

137 In France, a network of pediatric and adult clinical units along with laboratories in every
138 university medical center dedicated to the management of patients with PID (CEREDIH) has
139 been created in 2005. A national registry documenting information on patients with PID has
140 been created since then (5). National guidelines for care of both pediatric and adult patients
141 with PID have been developed and updated, while regular videoconferences ensure
142 harmonization on procedures and therapeutic indications at the national level (6). On this
143 background, and given the paucity of overall information on the occurrence of non-infectious
144 manifestations in PID patients over time, we decided to analyze data from a retrospective
145 cohort of 1375 unselected patients with PID followed over a 10-year period (i.e. 2009 to 2018)
146 in France. The analysis shows that non-infectious complications, i.e.
147 allergy/autoimmunity/inflammation and cancer occur with a relatively high frequency across
148 all ages and PID categories. These results call for further perspective assessment of their
149 occurrence in various PIDs and potential therapeutic actions.

150

151

152 **Methods**

153

154 Since December 2005, the French National Reference Center for PID (CEREDIH) runs a national
155 registry for documenting prevalent, incident as well as deceased patients diagnosed with a
156 PID with the exception of severe congenital neutropenia that is covered by an independent
157 registry (see Ref 5 for detailed methodology) (5). Relevant information is collected from
158 patients' electronic charts on local visits to University Hospital covering all France by full-time
159 dedicated and trained data entry clerks and then documented in the European Society for
160 Immunodeficiencies (ESID) registry (7). Follow-up documentations are performed on a regular
161 basis, once every 2 years on average.

162 The current study included patients recorded in the registry before 2009 January 1st
163 and alive by this date and living in France with a follow up to 2018 December 31st. Lost to
164 follow-up patients, defined as patients with no news after 2015 December 31st, were excluded
165 (**Suppl. Fig1**). Information including patient demographics, way to diagnosis, clinical diagnosis,
166 genetic diagnosis, occurrence of major clinical events such as allergy,
167 autoimmunity/inflammation or malignancies, therapies (Immunoglobulin replacement
168 therapy (IgRT) or curative such as Hematopoietic stem cell transplantation (HSCT), thymic
169 transplantation or gene therapy) and causes of deaths were retrieved from the database.
170 Infectious events were not analyzed in detail in this study.

171 Patients were classified in broad PID groups including (i) B cell deficiencies (common
172 variable immunodeficiency CVID and non CVID), (ii) T cell deficiencies including severe
173 combined immunodeficiencies (SCID), combined immunodeficiencies (CID), Wiskott-Aldrich
174 Syndrome (WAS), Hyper-IgE syndrome (HIES), Ataxia-Telangiectasia (AT), (iii) Hemophagocytic
175 lymphohistiocytosis (HLH) or other PID with predominant Immune dysregulation features and
176 (iv) Innate immune deficiencies (defined as all PID affecting the innate immune system except
177 chronic granulomatous disease (CGD) which is specifically described). Of note, patients could
178 have multiple causes concurring to death. Ages at events are ages at first occurrence of events
179 in the defined period of time. The national registry database (7,973 patients) was exported on
180 March 9th, 2020, for data management and quality control. All statistical analyses were
181 performed on R software version 3.6.1 (R Core Team (2018)). Categorical variables and
182 continuous variables were compared by Chi2 test or Mann-Whitney test, respectively. Risk

183 factors of death were analyzed using logistic regression method. Ninety-five percent
184 confidence intervals were calculated using the profile-likelihood approach.

185 From a population of 1,577 patients alive on January 1st, 2009, 202 were excluded for
186 lack of completion of follow up information. No striking difference in terms of age and
187 diagnosis was noticed between this group and the other cases (***Suppl Figure 1 and Suppl Table***
188 ***1***). Overall, a population of 1375 patients met the inclusion criteria. They include 1163 patients
189 who did not undergo a curative therapy (encompassing HSCT, gene therapy and thymic
190 transplantation) and 212 who underwent a curative therapy prior to the study starting point
191 (January 1st, 2009). These populations were accordingly analyzed separately. Global
192 information on these cohorts is given in ***Table 1 and Supplementary Table 2, Supplementary***
193 ***Table 3a and 3b***, including age, diagnosis, frequency at which these patients underwent
194 relevant events for the study (i.e., cancer, autoimmunity/inflammation, allergy events) prior
195 to January 1st, 2009.

196

197 **Results**

198 As shown in **Figures 1a-c**, and **Table 2**, 37% of patients with no previous curative
199 therapy from the cohort experienced before 2009 an "event", i.e. allergy, autoimmunity,
200 inflammation or cancer during their life time. In the 10-year period study, 20.1% patients
201 experienced a non-infectious event (**Table 2**). These data illustrate how frequent are such non-
202 infectious manifestations in PID patients. Together 16.1% of patients who did not have any
203 event prior to 2009 (n=97) developed such a complication within the 10-year period (**Figure**
204 **1b**). These events have occurred at all ages with a relatively similar frequency (**Figure 1c**). All
205 PID groups are affected although frequency varies somewhat between them (**Figure 1d**). In
206 total, 277 events occurred in 223 patients within the 10-year period, leading to a risk of 0.024
207 event/year/patient (**Figure 1e-g**). A summary of events that occurred during the 10-year
208 period is provided in **Table 2** and a detailed account as a function of PID diagnosis is depicted
209 in **Suppl Table 4**.

210 A total of 195 patients (14.2%) died within this 10-year period including 175 of patients
211 without a curative therapy and 20 (9.4%) of patients who previously received a curative
212 therapy. Kinetics of death events of patients with no previous curative therapy is shown in
213 **Figure 2**. Death rate was unsurprisingly higher in older patients but was quite high (9 up to
214 16.8%) over all age groups (**Figure 2b**). Risk of death was particularly high in the group of
215 patients with AT because of the very high incidence of cancer (see below). However, fatal
216 events occurred in all groups of patients (**Figure 2c**). Age and underlying cause of deaths as a
217 function of PID group are depicted in **Table 3**. Of note, non-infectious events accounted for
218 43% of deaths with an identified cause. Malignancy accounted to 22.4% of cases (34.2% of
219 deaths with an identified cause), which is a considerable frequency. Besides AT, cancer
220 occurred in 11 CVID patients out of 329 (3%) and 5 CID patients out of 193 (2.5%).

221 Fourteen percent of patients from the cohort had allergic events prior to 2009
222 confirming the known high frequency of allergy in PID patients. This was incremented by
223 another 2% of patients who developed allergy within the 10-year study period (**Figure 3 and**
224 **Suppl figure 2**). Onset of allergic events spanned all age classes showing that these might
225 occur during all adulthood (**Figure 3b**). Distribution as a function of PID diagnosis was broad,
226 although known PID groups prone to allergies (HIES, WAS, CID) were slightly overrepresented
227 together with CGD (**Suppl table 2**). The different categories of allergic events and their
228 frequency are indicated in **Suppl Table 5**.

229 Autoimmunity and inflammation are well-established features of PID. This is illustrated
230 by the fact that 22.8% patients had such manifestations prior to 2009 (**Figure 4**). Strikingly,
231 another 6.5% of patients developed these manifestations (**Suppl figure 3**) over the 10-year
232 follow up. Altogether 135 events were noted in this 10-year period. Age distribution shows an
233 apparent peak in the 11-30 years age category with a decline thereafter. Patients from all PID
234 groups have developed such manifestations, with a notable peak of inflammation events,
235 mostly digestive in CGD patients illustrating how frequent these complications are. Categories
236 and frequency of autoimmune/inflammatory manifestations are depicted in **Suppl Table 6**. As
237 shown in **Suppl Figure 4a,b**, occurrence of autoimmune/inflammatory manifestations either
238 before 2009 or between 2009-2018 was a death risk factor ($p=0.00045$).

239 This cohort study clearly shows the high risk of cancer in patients with PID since 6.2%
240 (85 patients) have developed a cancer during the 10-year study period (**Figure 5, Suppl figure**
241 **5**). Detailed list of malignancies is given in **Suppl Table 7**. There was an equal risk of
242 hematological malignancies and solid tumors. Interestingly enough, the risk of the former was
243 equally distributed overall all ages while the risk of solid tumors sharply increased with age
244 (**Figure 5b**). AT patients were, as expected, mostly affected by the occurrence of cancer
245 (**Figure 5c**). Nevertheless, virtually all PID groups were at risk for hematological malignancies
246 (mostly lymphomas) with the notable exception of patients with CGD. Solid tumors occurred
247 in patients with CVID, but also T-cell immunodeficiencies (CID). Not surprisingly, cancer was
248 associated with a higher death toll (**Suppl figure 4c,d**).

249 Malignancy (OR: 5.62 [3.66 – 8.62], $p<0.001$) and autoimmunity (OR: 1.90 [1.27 – 2.84],
250 $p=0.002$) were found to be significantly associated with an increased risk of death. Close to
251 40% of patients with malignancy died within the 10-year period (**Suppl figure 4c**). No
252 significant association has been observed between allergy and risk of death (OR: 0.85 [0.50 –
253 1.40], $p=0.536$).

254

255 **Curative therapy**

256 When analyzing occurrence of events in patients who underwent a curative treatment
257 of PID before 2009 ($n=212$, out of whom 180 patients with documentation, see **Suppl. Table**
258 **8**), an event occurred in 8.9% of them ($n=16$) including cancer ($n=7$), autoimmunity ($n=9$) and
259 allergy ($n=2$) (**Table 2**). Overall, 20 patients died, causes being shown in **Suppl Table 8, Suppl**
260 **Fig 3 and Suppl Fig 6**.

261 In part, because of occurrence of these serious complications and as a function of PID
262 diagnosis 71 patients (5.6%) underwent HSCT in this 10-year period (**Table 2**). PID categories
263 are as follows: CVID: 1, CID: 26, WAS: 9, immune dysregulation: 1, HLH: 9, SCID: 6 and innate
264 deficiencies: 19 out of whom 18 CGD. Median age at HSCT was 15.6 years (Q1;Q3: 8.4;23.3).
265 Median age at last news was 17.6 years (Q1;Q3: 13.7;27.8). Median post HSCT follow-up is 2.3
266 years (Q1;Q3: 0.7;6.2). Eight patients (11.3%) died after HSCT.
267
268

269 **Discussion**

270 In this study, we report on the occurrence of non-infectious complications in a large,
271 unselected cohort of patients with PID who were under care in France for a continuous 10
272 year-period. To our knowledge, this is the first study of this kind. It was made possible by the
273 continuous and updated documentation in a national registry of patients with PID who
274 underwent homogenous care and management including diagnostic methods, treatment of
275 complications as well as indication and implementation of curative therapy based on
276 indication on guidelines (6,8–10) and regular multidisciplinary meetings including transition
277 care (11–13).

278 There are several limitations to such a study since a small fraction of patients were lost
279 to follow up or information could not be retrieved over the 10-year period. Nevertheless, it
280 appears that the study population did not differ extensively from the overall PID population
281 of the national registry, thus making unlikely a selection bias. This study focuses on non-
282 infectious complications named as events in this manuscript, and their impact on survival. It
283 would be of obvious interest to perform similar studies encompassing all patients' medical
284 history including infectious events and also including quality of life assessments – a key issue
285 for patients with PID (14,15). Based on the CEREDIH registry, there is an ongoing collection of
286 these pieces of information to be later analyzed.

287 Nevertheless, as it stands, this study provides information on the relative frequency of
288 non-infectious events, as a function of age and PID diagnosis. It is an extension to previous
289 reports (16–20) including ones on the advent of allergy (21), autoimmune and inflammatory
290 disorders (3,22,23) and cancer across various PID (24–27). All age classes are affected albeit
291 distinctly and almost none of the PID diseases are spared for the advent of such complications
292 all along life span. It is translated into a significant risk of deaths that should definitively be
293 considered for therapeutic decision. The literature is rich in reports about the occurrence of
294 major non-infectious events and risk of deaths in patients with CVID (16,17,25,26,28,29).
295 Although there is a heterogeneity of PID category distribution of patients with
296 autoimmunity/inflammation across age classes, the present report nevertheless shows that
297 many more PID during childhood and adulthood carry a risk of immunopathological
298 comorbidities as a consequence of their disease. Of course, this type of study cannot replace
299 disease-specific assessment of clinical outcome as exemplified (13,30,31), that can much
300 better detect the specific features of the many known and less well known PID. However, this

301 study provides an estimation of the global burden of such complications in the setting of
302 specialized care of PID and the payload in terms of fatal risk.

303 Not surprisingly, cancer appears as a key prognostic factor for death as previously
304 reported for CVID (16,24,25,27). Most patients experienced one malignancy. Malignancies
305 occurred at all ages and in all PID categories. Median age at first malignancy is 35.3 years. PID
306 categories with the highest frequency of malignancies were B cell deficiencies (both CVID and
307 nonCVID) and AT. Hematological malignancies were prominent, with a higher frequency of
308 Non-Hodgkin lymphoma, followed by Hodgkin lymphomas, leukemias, myelodysplastic
309 syndromes and plasma cell disorders. Solid tumors were mostly skin cancers, digestive tract
310 cancers, breast cancers, thymoma, genital organ cancers and urinary tract cancers. These
311 findings call for a prospective surveillance of relevant patients for occurrence of such
312 malignancies. Mechanisms underlying cancer risk in PID are numerous, likely accounting for
313 the age distribution and type of cancer. They include defective DNA repair of pro-oncogenic
314 somatic mutations (AT, NBS...), poor handling of oncogenic viruses (i.e. EBV, HHV8, and
315 possibly HPVs) mostly in patients with T-cell immunodeficiencies, defective control of cell
316 death (ALPS...), repeated and/or protracted immune activation by micro-organisms leading to
317 the generation of DNA errors along cycles of cell division (potentially all PID causing
318 vulnerability to infections). Immunosenescence on top of immunodeficiency itself may
319 contribute as well as accumulation of somatic mutation in various tissues (24). Data indicate
320 that type of cancer, i.e. hematological malignancies, mostly lymphomas and solid tumor, occur
321 at different ages as a function of underlying disease and likely pathophysiological mechanism,
322 but in any case with a frequency much higher than in the study cohort compared to the whole
323 registry ($p=0.003$, See **Suppl. Table 1**).

324 The study also provides a picture of the related proportion at a nationwide level of
325 patients who underwent a curative therapy (mostly HSCT) in this 10-year period, i.e., in 5.6%
326 of the cohort. As expected, HSCT was performed in classical PID categories i.e., T-cell
327 immunodeficiencies, HLH and CGD and was mostly performed in children although some adult
328 patients were also transplanted (manuscript in preparation) (32,33).

329 Another interesting piece of data retrieved from this study is the follow-up of patients
330 who underwent curative therapy (mostly HSCT) prior to the study period. Amongst the 212
331 patients followed for 10 years, a fraction 8.9% (versus 20.1% in the cohort of patients who did
332 not receive curative therapy before 2009) still had some significant events that were not all

333 consequences of recent transplantation. This shows that late complication of HSCT, persisting
334 symptoms of PID, sequelae of pre HSCT manifestations or syndromic features of complex PID
335 can contribute significantly to post therapeutic morbidity and mortality (34,35). Such an
336 observation is an incentive to plan a prospective study carefully assessing the long-term
337 outcome of HSCT for PID as a function of all these parameters. Indeed, we propose that
338 patients with PID developing autoimmunity should be considered for curative therapy as very
339 significant advances in these procedures have been made in the past decades, including for
340 teenagers and adults with CGD, CID or WAS, amongst other PID categories. For patients with
341 PIDs such as CTLA4, LRBA, APDS1/2, targeted therapies now play a very important role in the
342 management of these patients (32). Hence, performing a genetic documentation (using NGS
343 techniques, including panels) is of utmost importance in providing the best level of care for
344 patients with PID (8).

345 The aim of our manuscript was to provide a descriptive observational analysis of the
346 major comorbidities occurring in a large cohort of patients with PID followed up in a national
347 reference network. This study reflects on the severity and complexity of care of PID patients.
348 It calls a) to emphasize the need that every single PID patient benefits from the care from a
349 multidisciplinary team of experienced healthcare professionals and b) to design prospective
350 refined studies analyzing as a function of time the PID patients' history under optimal care,
351 including comparison with control groups.

352

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511 **Figure 1: Frequency at which patients developed events during the 10-year follow-up period**
512 **and frequency of events**

- 513 a. Cumulative percentage of patients who experienced at least one event before 2009
514 and since January, 1st 2009 (n=1163)
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516 period (2009-2018) (Percentages are calculated on the 603 patients who never
517 experienced any event before 2009)
- 518 c. Fraction of patients who experienced at least one event during the study period (2009-
519 2018) according to age class in 2009 (n=1163)
- 520 d. Fraction of patients who experienced at least one event during the study period (2009-
521 2018) by PID category (n=1163)
- 522 e. Cumulative number of events during the study period (2009-2018)
- 523 f. Number of events that occurred during the study period (2009-2018) according to age
524 class in 2009
- 525 g. Number of events that occurred during the study period (2009-2018) by PID category

526

527 **Abbreviations:**

528 AT: ataxia telangiectasia; CGD: chronic granulomatous disease; CID: combined
529 immunodeficiency; CVID: common variable immunodeficiency; HIES: hyper immunoglobulin
530 E syndrome; HLH: hemophagocytic lymphohistiocytosis; ImDysReg: immune dysregulation;
531 SCID: severe combined immunodeficiency; WAS: Wiskott Aldrich syndrome

532

533 **Figure 2: Death events**

- 534 a. Cumulative percentage of deaths (cohort, n=1163)
- 535 b. Fraction of deaths according to age class in 2009
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537

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- 539 a. Cumulative percentage of patients who experienced at least one allergy event during
540 the study period (2009-2018) among 1023 evaluable patients

541 b. Fraction of patients who experienced at least one allergy event during the study period
542 (2009-2018) according to age class in 2009

543 c. Fraction of patients who experienced at least one allergy during the study period
544 (2009-2018) event by PID category

545 Only pre-curative therapy events are considered.

546

547 **Figure 4: Autoimmunity/inflammation events**

548 a. Cumulative percentage of patients who experienced at least one
549 autoimmunity/inflammation event during the study period (2009-2018) among 1025
550 evaluable patients

551 b. Fraction of patients who experienced at least one autoimmunity/inflammation event
552 during the study period (2009-2018) according to age class in 2009

553 c. Fraction of patients who experienced at least one autoimmunity/inflammation event
554 during the study period (2009-2018) by PID category

555 Only pre-curative therapy events are considered.

556

557 **Figure 5: Malignancy events**

558 a. Cumulative percentage of patients who experienced at least one hematological
559 malignancy and/or solid tumor during the study period (2009-2018) among 1151
560 evaluable patients

561 b. Fraction of patients who experienced at least one hematological malignancy and/or
562 solid tumor during the study period (2009-2018) according to age class in 2009

563 c. Fraction of patients who experienced at least one hematological malignancy and/or
564 solid tumor during the study period (2009-2018) by PID category

565 Only pre-curative therapy events are considered.

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573

574 **Table 1: Patients characteristics at baseline, January, 1st 2009.**

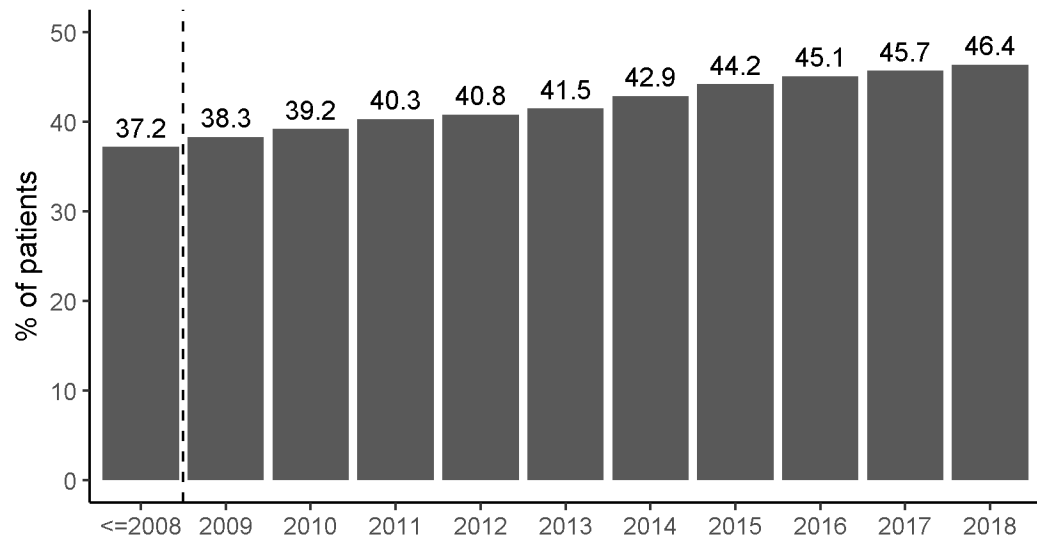
575

576 **Table 2: Patients with events during the study period (2009-2018).**

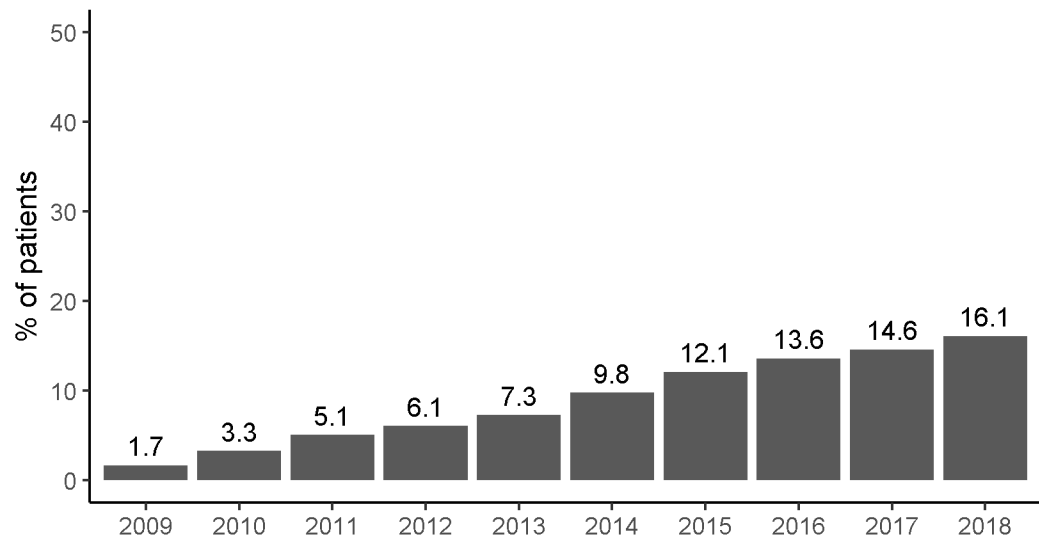
577

578 **Table 3: Causes of deaths.**

a. At least one event



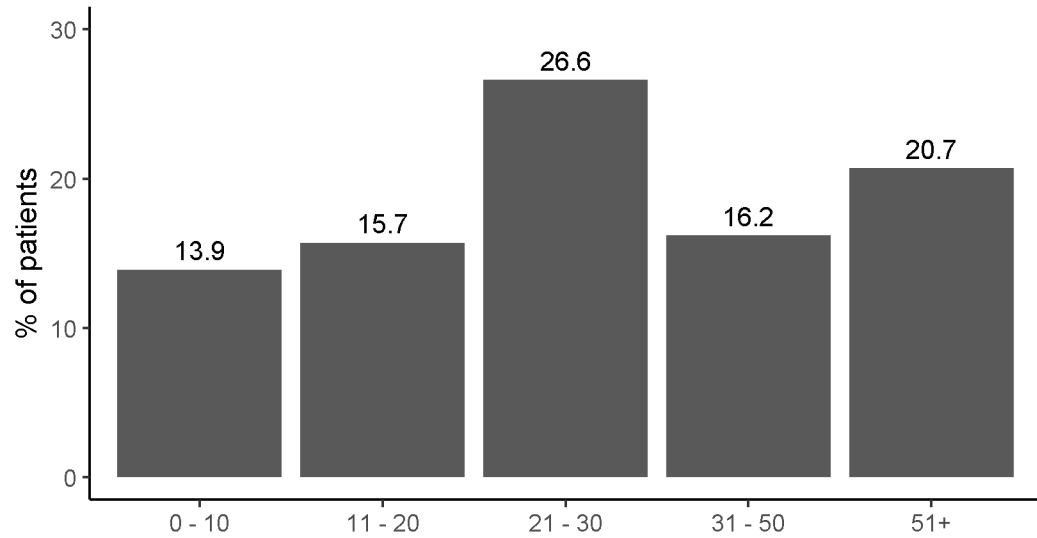
b. Occurrence of a first event



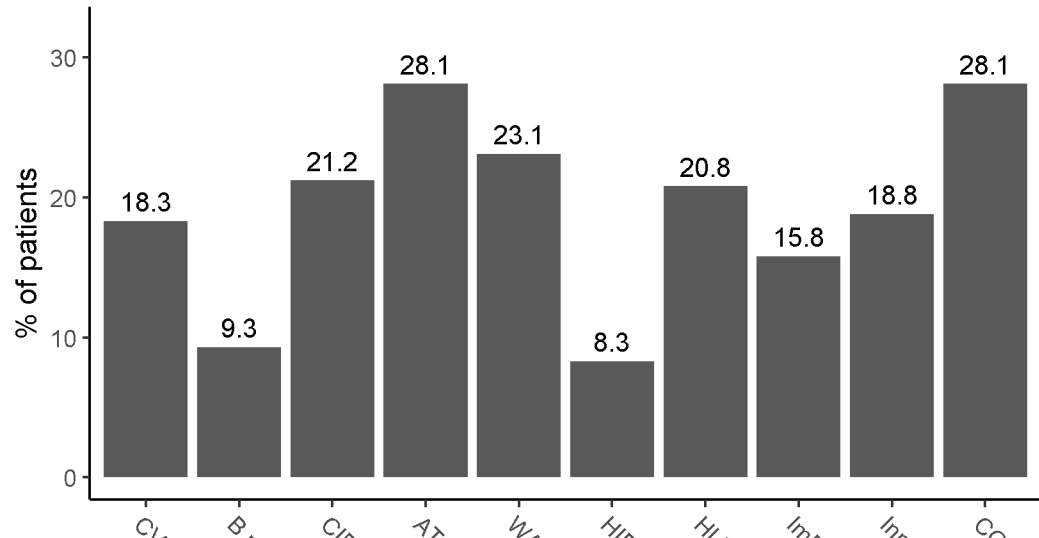
Years

Years

c. At least one event



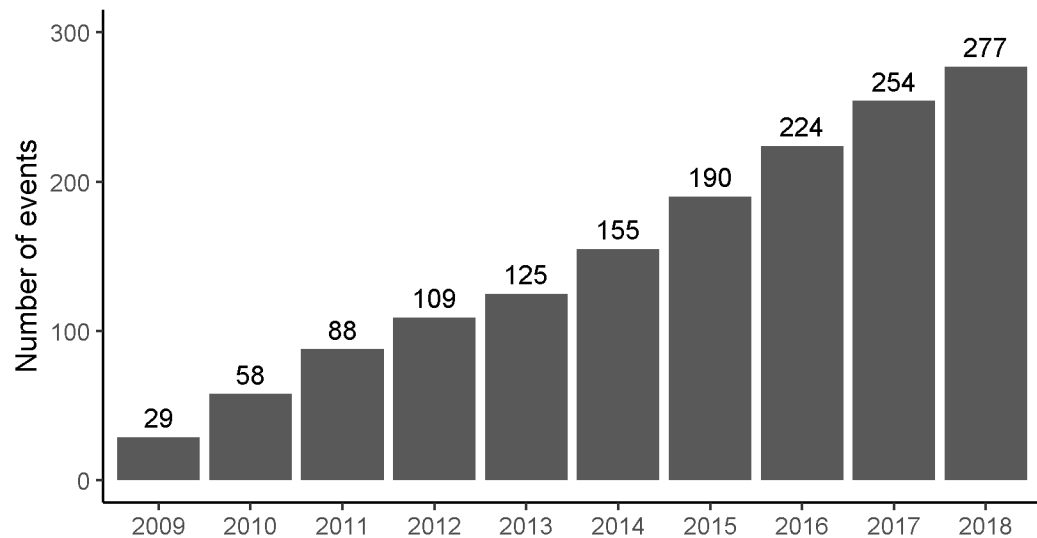
d. At least one event



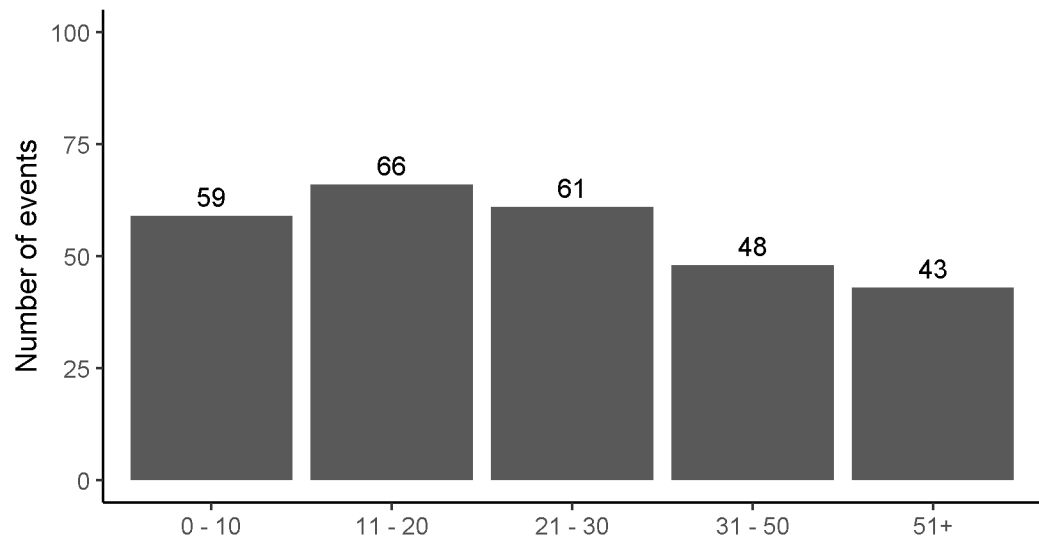
Age class in 2009 (years)

PID category

e. Cumulative number of events



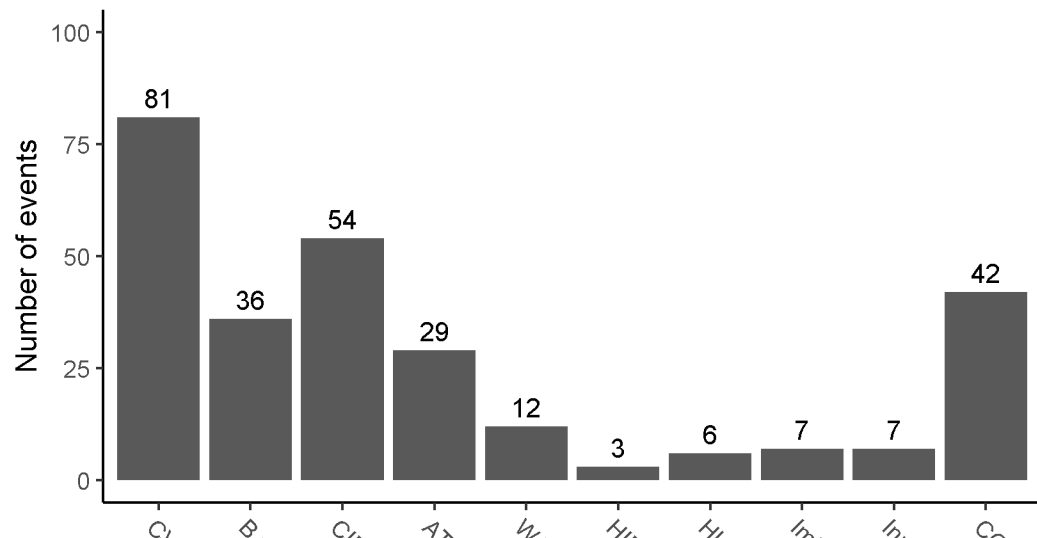
f. Number of events



Years

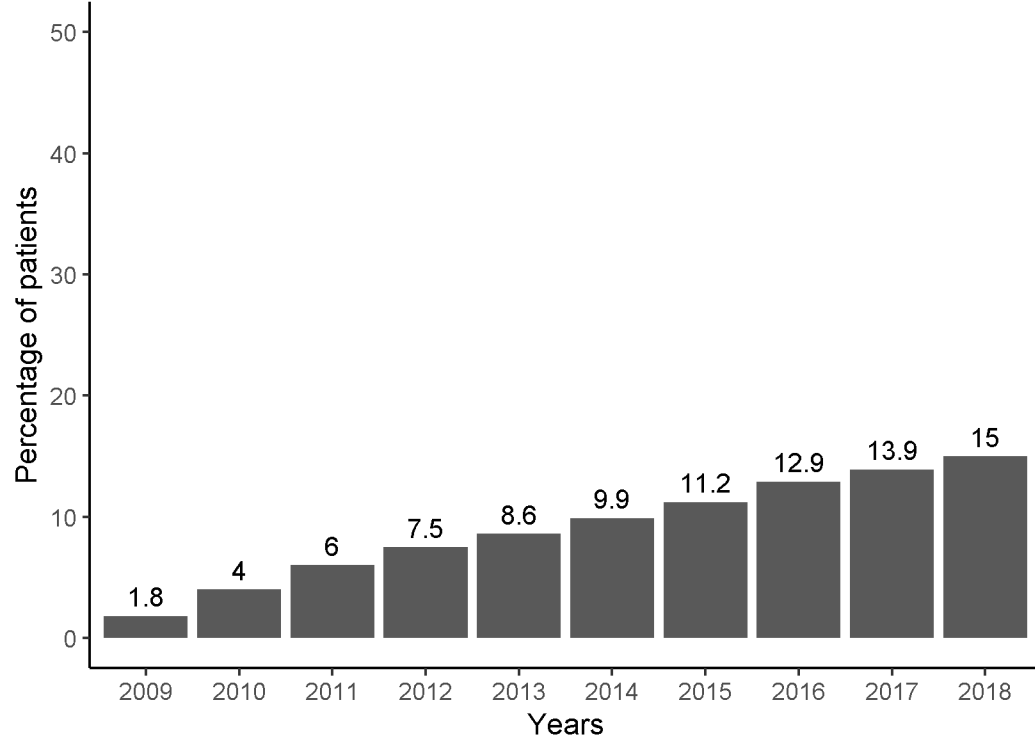
Age class in 2009 (years)

g. Number of events

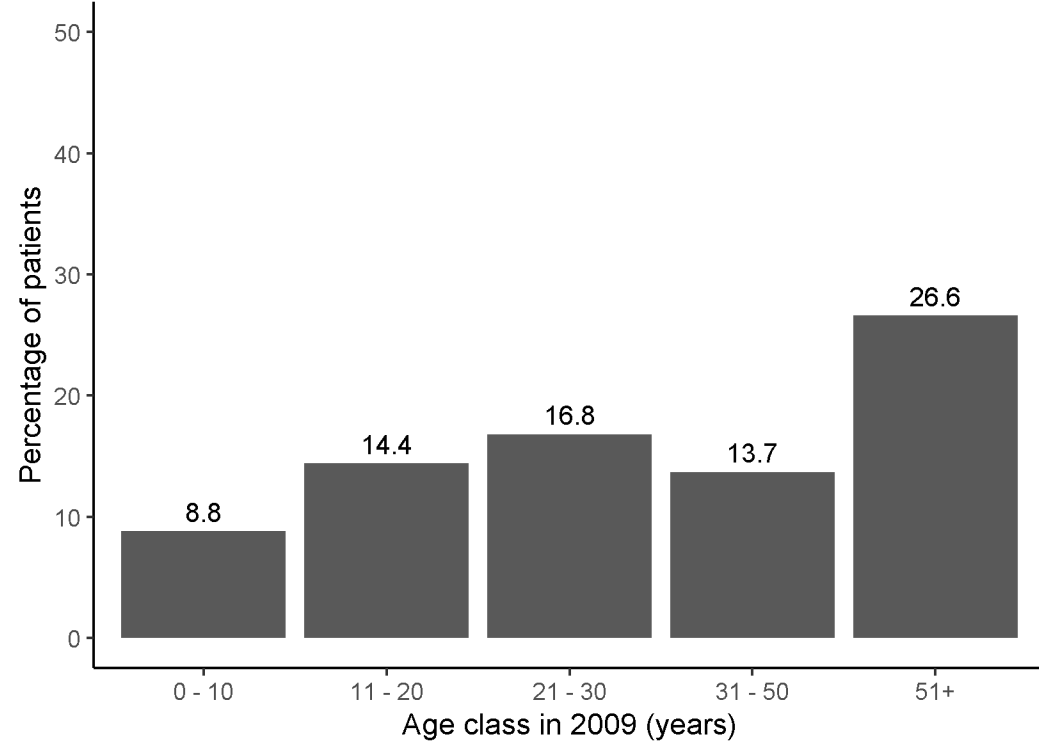


PID category

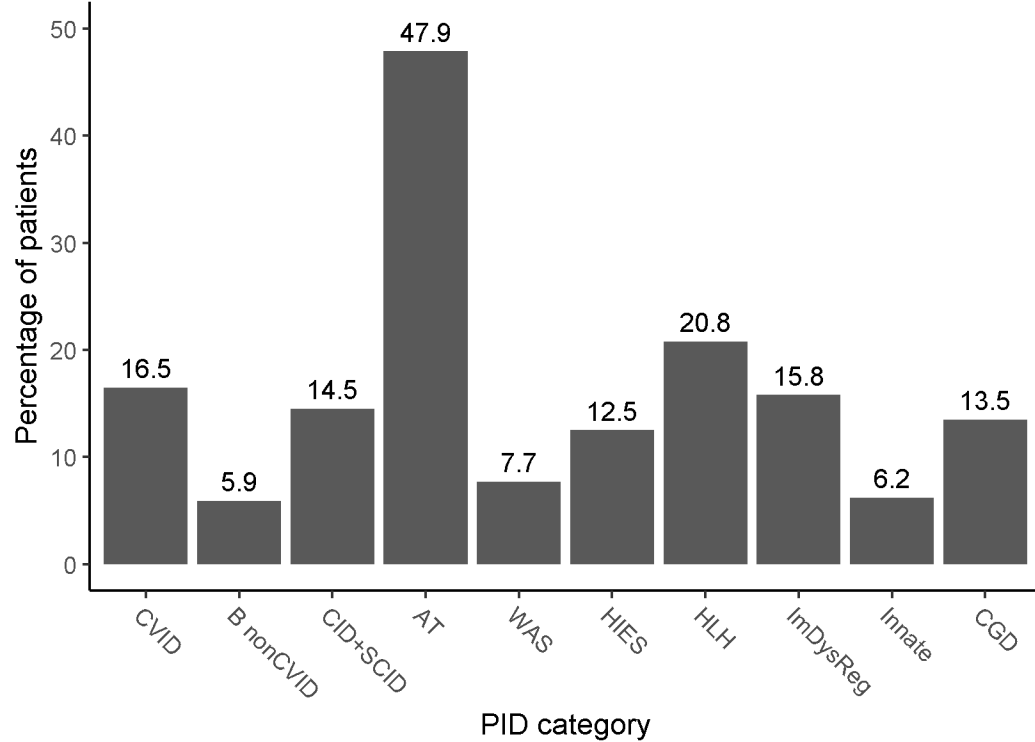
a. Cumulative percentage of deaths



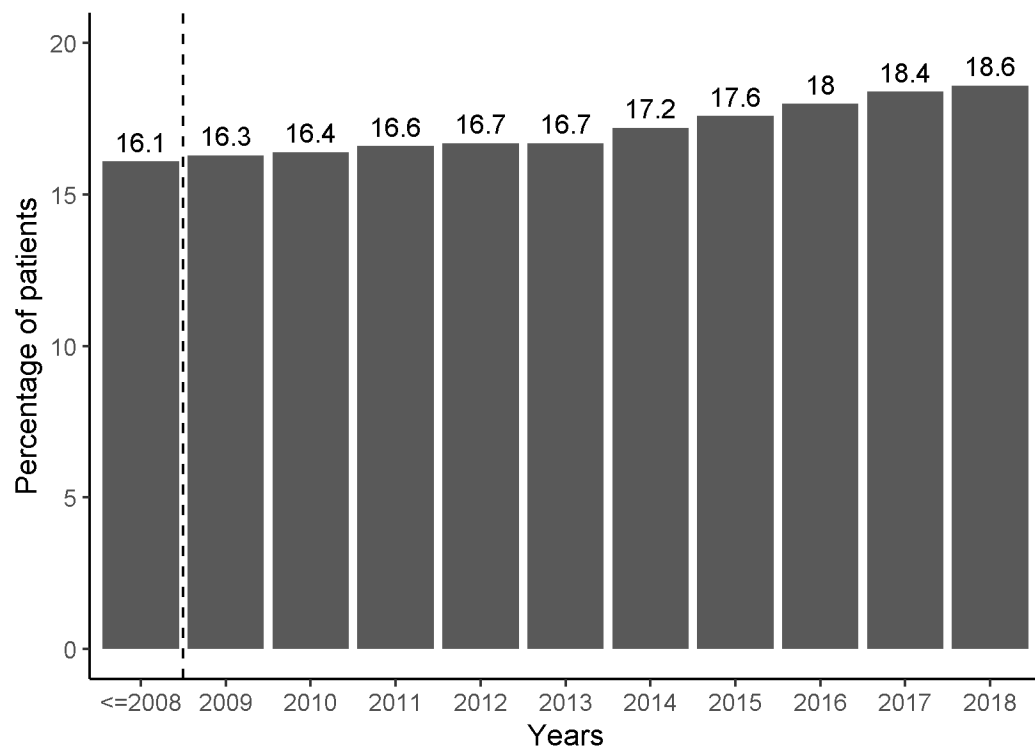
b. Fraction of deaths



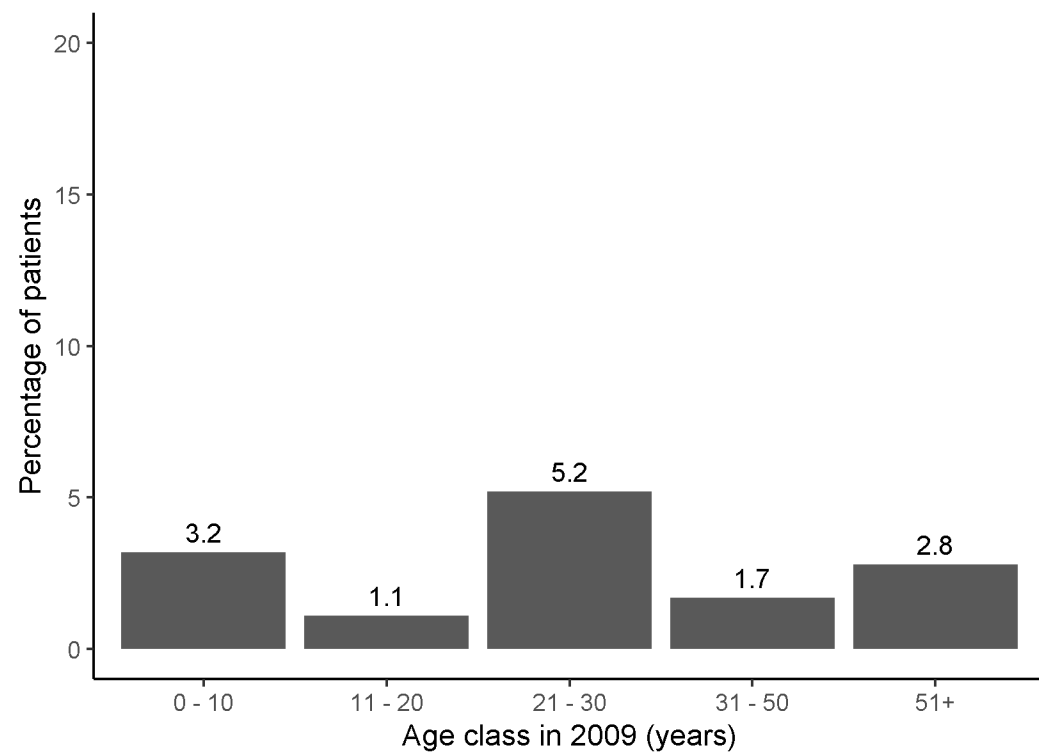
c. Fraction of deaths



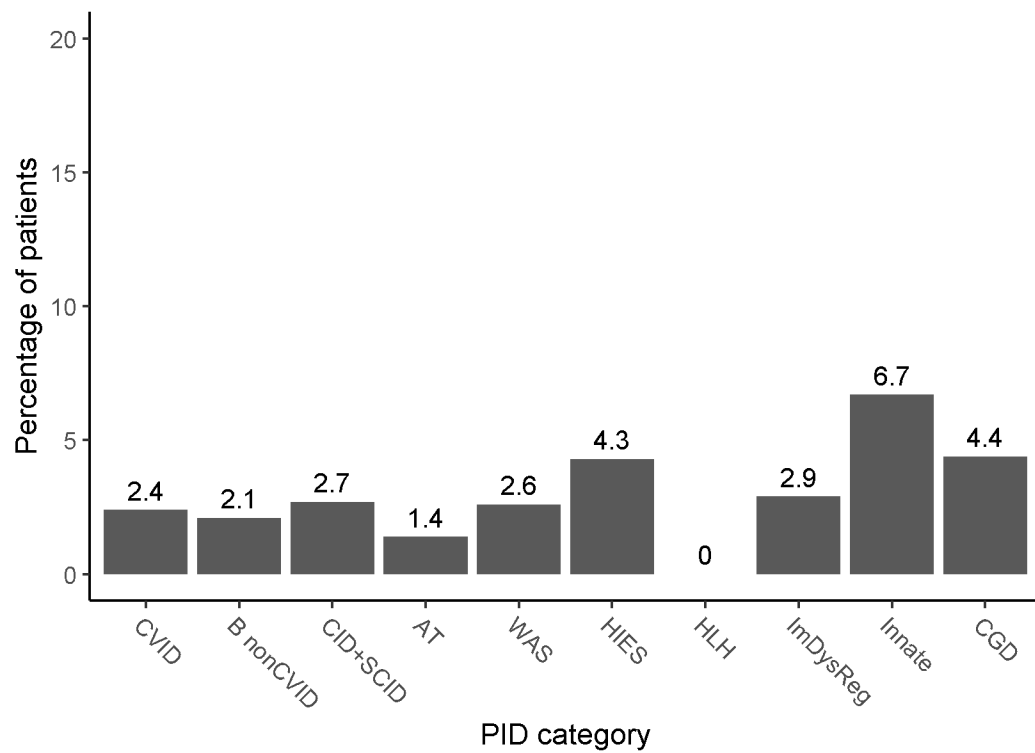
a. Cumulative percentage of allergy



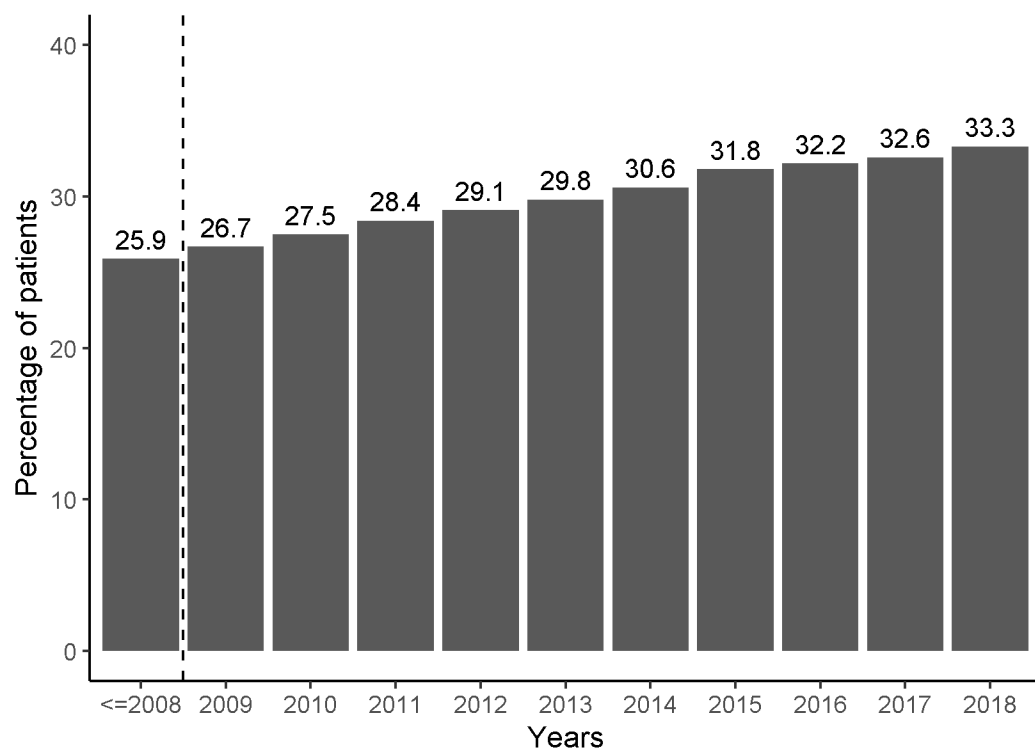
b. Fraction of allergy



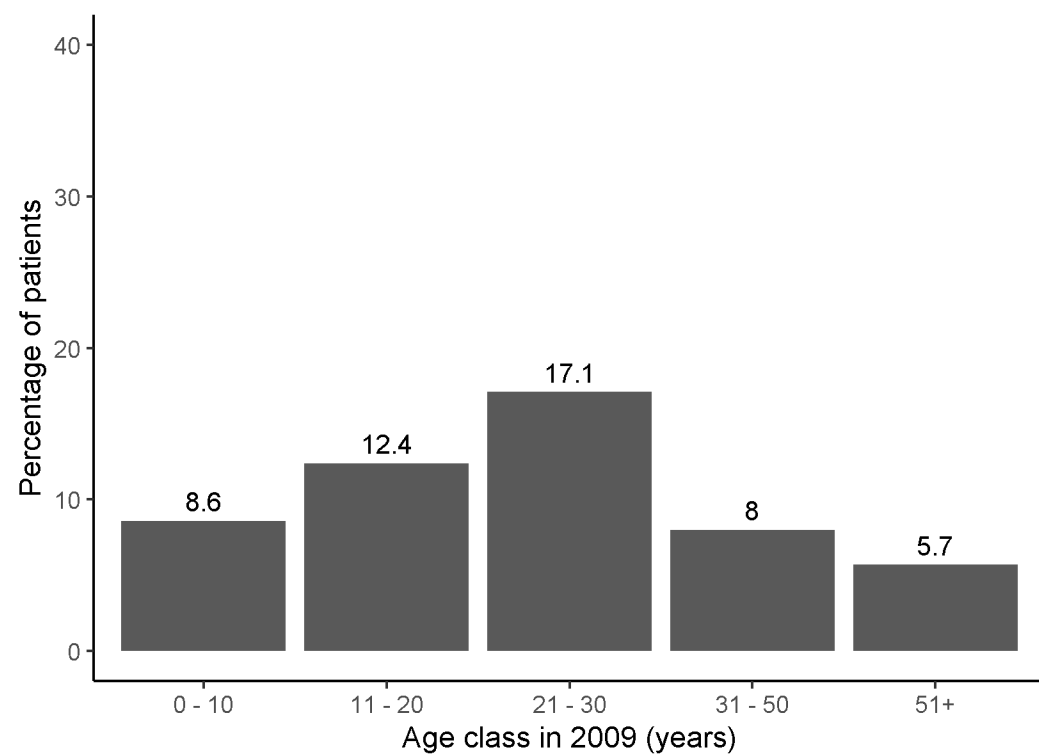
c. Fraction of allergy



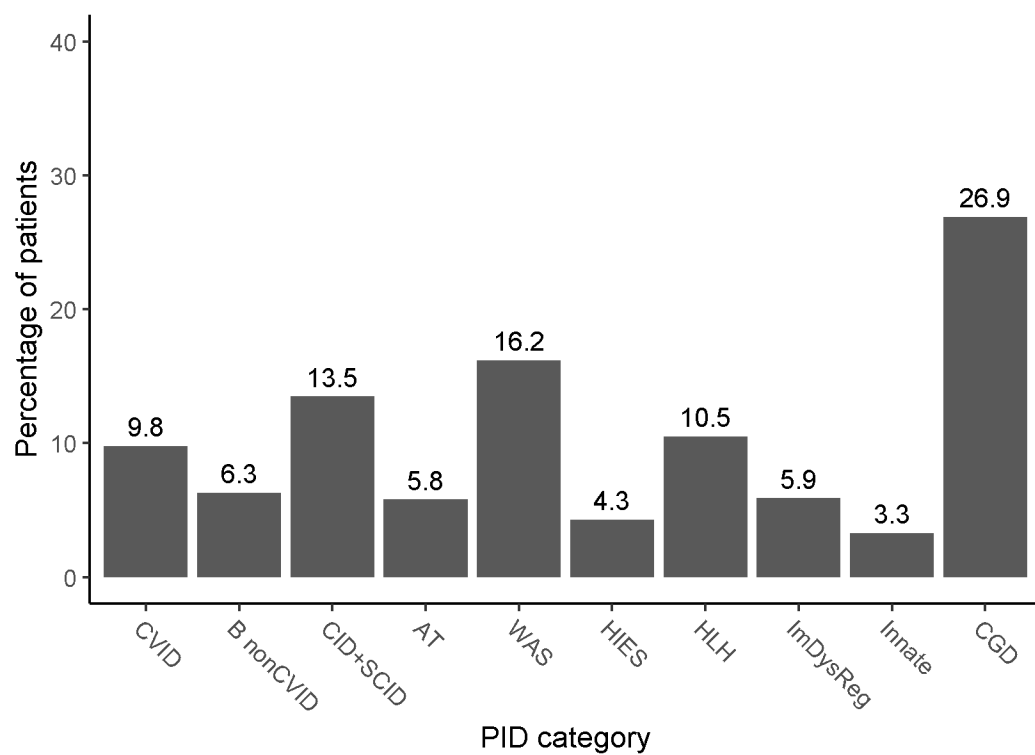
a. Cumulative percentage of AI/Infla



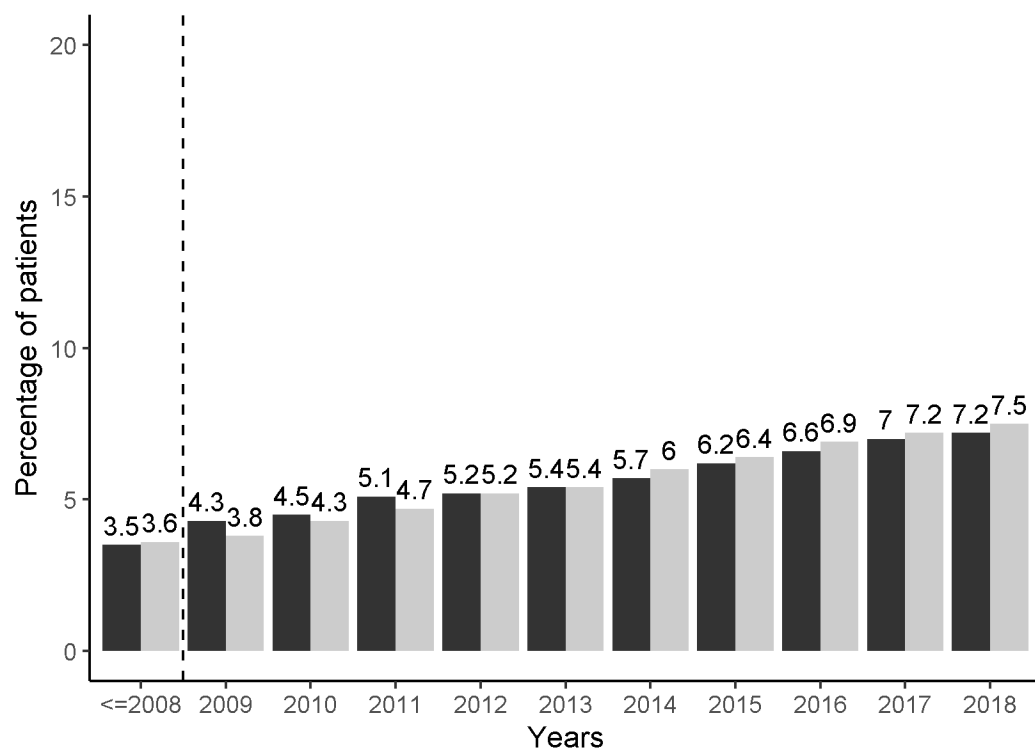
b. Fraction of AI/Infla



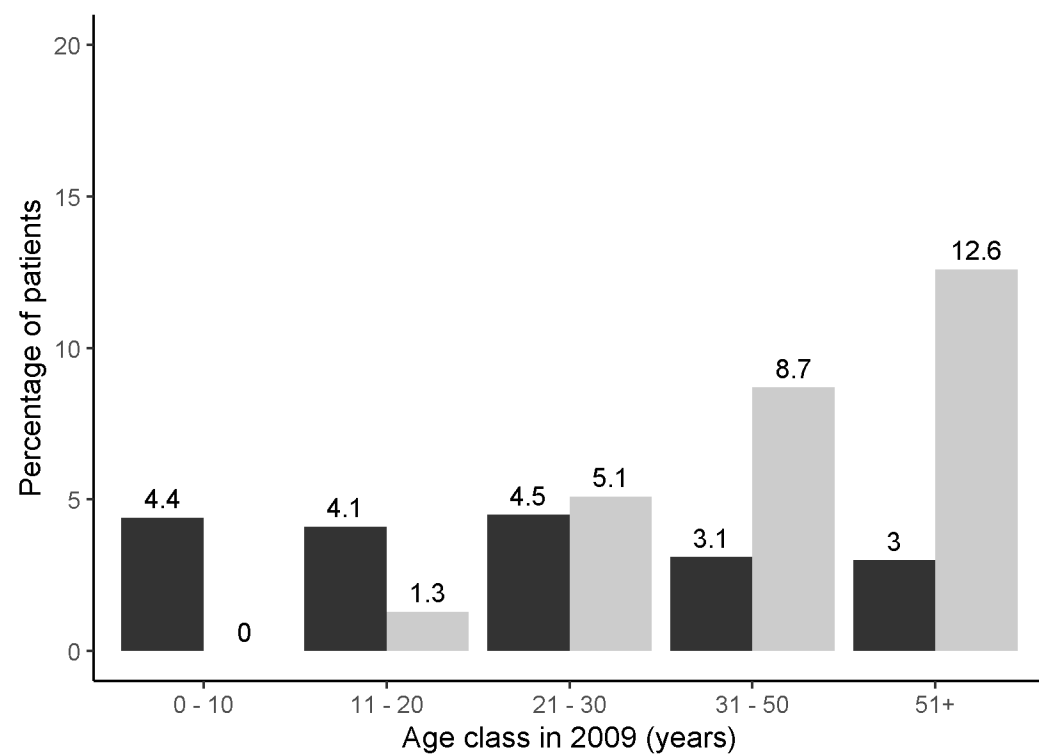
c. Fraction of AI/Infla



a. Cumulative percentage of malignancy



b. Fraction of malignancy



c. Fraction of malignancy

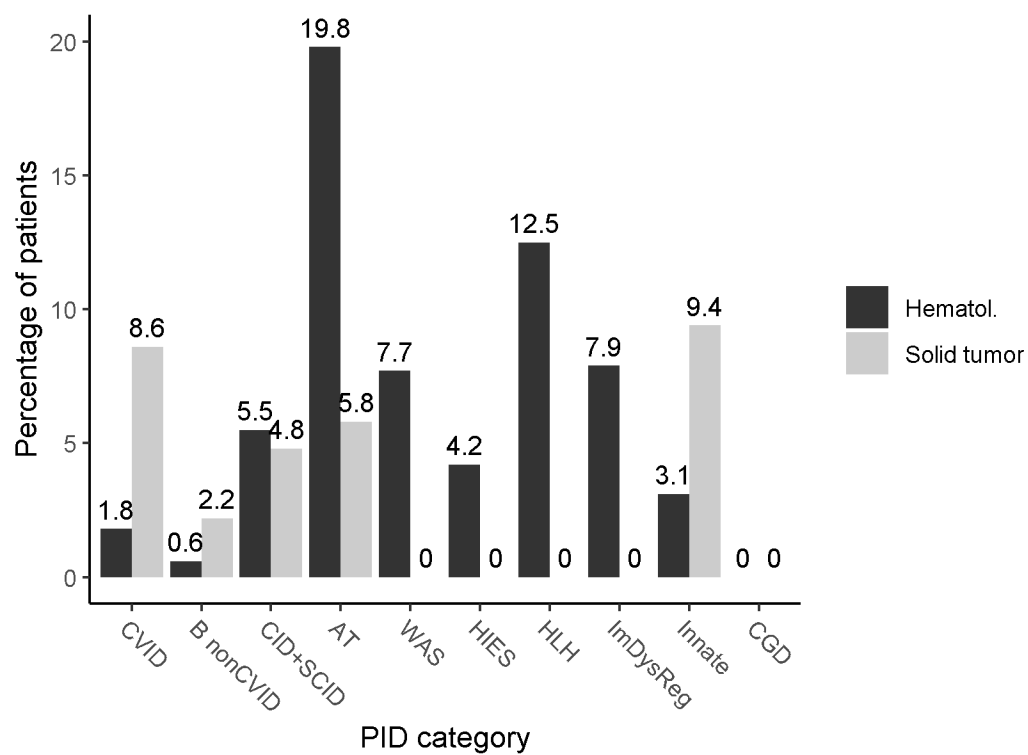


Table 1

Covariate	Values	Whole cohort	No curative therapy	Curative therapy
		N=1375	N=1163	N=212
Gender	F	516 (37.5%)	440 (37.8%)	76 (35.8%)
	M	859 (62.5%)	723 (62.2%)	136 (64.2%)
PID diagnosis	B CVID	329 (23.9%)	328 (28.2%)	1 (0.5%)
	B nonCVID	321 (23.3%)	321 (27.6%)	0 (0%)
	CID	193 (14%)	160 (13.8%)	33 (15.6%)
	AT	96 (7%)	96 (8.3%)	0 (0%)
	SCID	98 (7.1%)	5 (0.4%)	93 (43.9%)
	WAS	70 (5.1%)	39 (3.4%)	31 (14.6%)
	HIES	24 (1.7%)	24 (2.1%)	0 (0%)
	HLH	63 (4.6%)	24 (2.1%)	39 (18.4%)
	ImDysReg	41 (3%)	38 (3.3%)	3 (1.4%)
	Innate non CGD	35 (2.5%)	32 (2.8%)	3 (1.4%)
	CGD	105 (7.6%)	96 (8.3%)	9 (4.2%)
	Age at last news		26.9 [18.8;42.3]	28.4 [19.4;47.2]
Malignancy*	N	1271 (93.5%)	1072 (93.1%)	199 (95.7%)
	Y	88 (6.5%)	79 (6.9%)	9 (4.3%)
Hematol. malignancy*	N	1328 (96.6%)	1123 (96.6%)	205 (96.7%)
	Y	47 (3.4%)	40 (3.4%)	7 (3.3%)
Solid tumor*	N	1331 (96.8%)	1121 (96.4%)	210 (99.1%)
	Y	44 (3.2%)	42 (3.6%)	2 (0.9%)
Allergy	N	1008 (83.9%)	858 (83.9%)	150 (83.8%)
	Y	194 (16.1%)	165 (16.1%)	29 (16.2%)
Autoimmunity	N	915 (75.5%)	760 (74.1%)	155 (82.9%)
	Y	297 (24.5%)	265 (25.9%)	32 (17.1%)
All events	N	731 (60%)	603 (58.2%)	128 (69.9%)
	Y	488 (40%)	433 (41.8%)	55 (30.1%)
Ig replacement	N	528 (47.8%)	408 (43.1%)	120 (76.4%)
	Y	576 (52.2%)	539 (56.9%)	37 (23.6%)

Table 2

Covariate	Values	Whole cohort	No curative therapy (2009)	Curative therapy (2009)
		N=1375	N=1163	N=212
Living status	Alive	1180 (85.8%)	988 (85%)	192 (90.6%)
	Deceased	195 (14.2%)	175 (15%)	20 (9.4%)
Malignancy*	N	1260 (92.7%)	1058 (91.9%)	202 (97.1%)
	Y	99 (7.3%)	93 (8.1%)	6 (2.9%)
Hematol. Malignancy*	N	1312 (96.5%)	1106 (96.1%)	206 (99%)
	Y	47 (3.5%)	45 (3.9%)	2 (1%)
Solid tumor*	N	1303 (95.9%)	1100 (95.6%)	203 (97.6%)
	Y	56 (4.1%)	51 (4.4%)	5 (2.4%)
Allergy	N	1173 (97.6%)	996 (97.4%)	177 (98.9%)
	Y	29 (2.4%)	27 (2.6%)	2 (1.1%)
Autoimmunity	N	1096 (90.4%)	918 (89.6%)	178 (95.2%)
	Y	116 (9.6%)	107 (10.4%)	9 (4.8%)
All events**	N	987 (81.6%)	823 (79.9%)	164 (91.1%)
	Y	223 (18.4%)	207 (20.1%)	16 (8.9%)
Ig replacement	N	652 (91.8%)	602 (91.8%)	50 (92.6%)
	Y	58 (8.2%)	54 (8.2%)	4 (7.4%)
Route of Ig replacement***	IV	26 (55.3%)	25 (56.8%)	1 (33.3%)
	SC	21 (44.7%)	19 (43.2%)	2 (66.7%)
Curative therapy	N	1304 (94.8%)	1098 (94.4%)	206 (97.2%)
	Y	71 (5.2%)	65 (5.6%)	6 (2.8%)

Table 3

Covariate	Whole cohort	B CVID	B nonCVID	CID	AT	SCID	WAS	HIES	HLH	ImmDysReg	Innate nonCGD	CGD
	N=175	N=54	N=19	N=23	N=46	N=1	N=3	N=3	N=5	N=6	N=2	N=13
Age at death (y)	28.9 [18.6;57.6]	65 [50.2;74.2]	44.7 [20.7;72.5]	20.8 [14.6;26.6]	20.7 [16.4;26.8]	2.7 [2.7;2.7]	13 [12;19]	33.6 [31.3;34.6]	34 [23.1;35.1]	29.6 [23.5;48.1]	41.2 [33.7;48.7]	16.4 [14.8;31.2]
Infection	49 (28.2%)	11 (20.8%)	4 (21.1%)	9 (39.1%)	11 (23.9%)	1 (100%)	1 (33.3%)	2 (66.7%)	1 (20%)	0 (0%)	0 (0%)	9 (69.2%)
Immune dysr.	7 (4%)	2 (3.8%)	0 (0%)	2 (8.7%)	0 (0%)	0 (0%)	1 (33.3%)	0 (0%)	0 (0%)	1 (16.7%)	0 (0%)	1 (7.7%)
Malignancy	39 (22.4%)	11 (20.8%)	4 (21.1%)	5 (21.7%)	14 (30.4%)	0 (0%)	1 (33.3%)	0 (0%)	1 (20%)	1 (16.7%)	2 (100%)	0 (0%)
Transplantation related	14 (8%)	0 (0%)	0 (0%)	6 (26.1%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)	3 (60%)	1 (16.7%)	0 (0%)	3 (23.1%)
Other	29 (16.8%)	9 (17.3%)	3 (15.8%)	4 (17.4%)	7 (15.2%)	0 (0%)	0 (0%)	2 (66.7%)	0 (0%)	1 (16.7%)	1 (50%)	2 (15.4%)
Unknown	61 (35.5%)	27 (50%)	9 (47.4%)	4 (19%)	17 (37%)	0 (0%)	0 (0%)	0 (0%)	1 (20%)	2 (40%)	0 (0%)	1 (7.7%)