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AA Amyloidosis Secondary to Primary Immune Deficiency: About 40 Cases Including 2 New French Cases and a Systematic Literature Review

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► To cite this version:

Marion Delplanque, Lionel Galicier, Eric Oziol, Stéphanie Ducharme-Bénard, Eric Oksenhendler, et al.. AA Amyloidosis Secondary to Primary Immune Deficiency: About 40 Cases Including 2 New French Cases and a Systematic Literature Review. *Journal of Allergy and Clinical Immunology: In Practice*, 2021, 9 (2), pp.745-752.e1. 10.1016/j.jaip.2020.09.023 . inserm-04050271

HAL Id: inserm-04050271

<https://inserm.hal.science/inserm-04050271v1>

Submitted on 22 Jul 2024

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1 **AA amyloidosis secondary to primary immune deficiency: about 40 cases including 2 new**
2 **French cases and a systematic literature review.**

3

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26 **Authors disclose any financial relationship with a biotechnology and/or pharmaceutical**
27 **manufacturer that has an interest in the subject matter or materials discussed in the**
28 **submitted manuscript.** Each author has no conflict of interest to declare concerning this manuscript.

29 **Word count: Manuscript: 3075 words; Abstract: 243 words**

30

31 **Highlights box:**

32 1. What is already known about this topic?

33 **AAA is a long term complication of PID with a poor prognosis**

34 2. What does this article add to our knowledge?

35 **If AAA patient displays bronchiectasis, PID should be sought, especially humoral**
36 **deficiencies.**

37 3. How does this study impact current management guidelines?

38 **Renal function and proteinuria monitoring should be monitored among PID patients**

39

40

41 **Key words: Primary Immune deficiency, Common variable immunodeficiency, Humoral**
42 **deficiency, Long term complication, AA Amyloidosis, nephrotic syndrome, prognosis,**
43 **chronic infections, bronchiectasis, systematic review**

44

45

46

47 **Abbreviations**

48 AAA: AA Amyloidosis

49 BK: tuberculosis

50 CEREDIH: Reference Center for Hereditary Immune Deficiencies

51 CEREMAIA: Reference Center for Auto-Inflammatory Diseases and AA Amyloidosis

52 CGD: Chronic Granulomatous Disease

53 CRP: C-reactive protein

54 CT scan: Computerized tomography scan

55 CTC: Corticosteroids

56 CVID: Common variable immunodeficiency

57 DMARD: Disease-Modifying Antirheumatic Drugs

58 ESR: Erythrocyte sedimentation rate

59 F: Female

60 FMF: Familial Mediterranean Fever

61 GI: Gastrointestinal

62 HIES: Hyper IgE Syndrome

63 HIV: Human Immunodeficiency Virus

64 HPV: Human Papillomavirus

65 HSCT: Hematopoietic Stem Cell Transplantation

66 HSV: Herpes Simplex Virus

67 IM: Intramuscular

68 IRT: Immunoglobulin Replacement Therapy

69 IV: intravenous

70 LRBA: LPS Responsive Beige-like Anchor protein

- 71 M: Male
- 72 PAD: Predominantly Antibody Deficiency
- 73 PID: Primary Immune Deficiency
- 74 PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
- 75 RA: Rheumatoid arthritis
- 76 SAA: Serum Amyloid A
- 77 SC: Subcutaneous
- 78 TLR: Toll-Like Receptor
- 79 TTE: TransThoracic Echocardiography
- 80 VZV: Varicella-Zoster Virus
- 81 XLA: X-linked agammaglobulinemia
- 82 Yrs: Years
- 83

84 **Abstract (243 words)**

85 **Background:** Primary immune deficiencies (PID) are a heterogeneous group of disorders
86 resulting from defects in immune system. They lead to increased susceptibility to infections and
87 immune dysregulation. The resulting chronic inflammation can induce long-term complications,
88 including AA amyloidosis (AAA).

89
90 **Objectives:** To present the French cases of PID-related AAA and perform a systematic literature
91 review to determine its main features and predisposing factors.

92
93 **Methods:** A systematic literature review was performed by searching MEDLINE up until 2019.
94 New French cases were identified with the help of the Reference Center for Auto-Inflammatory
95 Diseases and AA Amyloidosis (CEREMAIA) and the Reference Center for Hereditary Immune
96 Deficiencies (CEREDIH).

97
98 **Results:** Forty patients were identified including 2 new French cases. PID were varied:
99 immunoglobulin deficits (n=30), chronic granulomatous disease (n=3), Hyper IgM syndrome
100 (n=3), hereditary complete C4 deficiency (n=1), Leucocyte Adhesion Deficiency Type-1 (n=1),
101 Hyper IgE syndrome (n=1) and Chediak-Higashi syndrome (n=1). Mean age at PID diagnosis
102 was 22.2 ± 16.02 years. Renal involvement was the most common manifestation of AAA (80%).
103 Infections were extremely heterogenous; bacterial infection with pulmonary involvement was the
104 most frequent. Bronchiectasis was particularly common (52,5%). The delay between the first
105 symptoms of PID and AAA diagnosis was 16.18 ± 7 years. Thirteen concomitant diagnoses were
106 made. Twenty patients died during follow-up.

107
108 **Conclusion:** AAA is a rare life-threatening complication of PID, especially in cases of long
109 diagnostic and therapeutic delays. Bronchiectasis should be considered as a warning sign of
110 chronic inflammation and increased risk of AAA.

111

112

113 **Introduction**

114 Primary immune deficiencies (PID) are a heterogeneous group of diseases. While several
115 classification systems exist, the one of the International Union of Immunological Societies (IUIS)
116 expert committee for Primary Immunodeficiency is the most frequently used (1,2). PID are
117 defined by an immune system failure with no underlying infectious, neoplastic or iatrogenic
118 cause (3), leading to increased susceptibility to infection and immune dysregulation. The
119 prevalence of PID in the general population is not well established, and probably underestimated
120 because of the heterogeneity of these diseases. While severe and potentially life-threatening PID
121 usually begin in the first weeks of life, others declare themselves later, including in adulthood.

122 More than 300 genes are associated with PID, causing mono or multigenic genetic abnormalities
123 (4). Common variable immunodeficiency (CVID) is a type of PID generally affecting adults and
124 characterized by impaired B cell differentiation resulting in hypogammaglobulinemia, normal or
125 low numbers of B cells, and poor antibody response (5).

126 AA amyloidosis (AAA) is a multisystemic disease related to the deposition of serum amyloid A
127 (SAA) protein secondary to chronic inflammation. Causes are multiple, the most frequent ones
128 being chronic rheumatic and inflammatory bowel diseases, monogenic autoinflammatory
129 diseases and chronic infections. However, immune deficiencies can also lead to AAA by
130 predisposing to infection (6,7). Chronic and recurrent infections as well as immune dysregulation
131 in patients with PID may lead to chronic inflammation, favoring extracellular deposition of SAA.
132 Numerous assumptions exist about predisposing conditions of AAA complicating PID: severity,
133 bronchiectasis, tuberculosis, delay in the diagnosis, delay of replacement therapy onset (8,9) but
134 to the best of our knowledge, there is no previous study on such association.

135 Our objective was to perform a systematic review of the literature and report of new French cases
136 to describe the characteristics of PID complicated by AAA, as well as risk factors and clinical
137 presentation of PID-associated AAA.

138

139 **Materials and Methods**

140 We conducted our systematic review using Preferred Reporting Items for Systematic Reviews
141 and Meta-Analyses (PRISMA) (10). No previously published research protocol was used. We
142 searched MEDLINE for all articles pertaining to AAA in PID. We selected published articles
143 indexed in PubMed involving humans and written in French, English or Spanish between 1946
144 and 2019. The keywords used were the following ones: (“Common Variable
145 Immunodeficiency”[Mesh] or “Severe Combined Immunodeficiency”[Mesh] or “Immune
146 Deficiency Disease” [Supplementary Concept] or “Immune Deficiency, Familial Variable”
147 [Supplementary Concept]) AND “Amyloidosis”[Mesh], “immune deficiency and amyloidosis”.
148 We chose to study only primary immunodeficiency, thus excluding immune deficiency secondary
149 to treatments, Human Immunodeficiency Virus (HIV), cancer or other diseases such as diabetes.
150 An independent investigator (MD) first screened titles and abstract to exclude duplicate and those
151 off-topic. Articles were then assessed for eligibility. Only full-text articles with detailed original
152 cases were selected. These cases could be embedded in any type of clinical study. Two hundred
153 sixty-two references were identified through database searching, and 44 articles were assessed for
154 eligibility.

155
156 French cases were identified using the CEREMAIA (Centre de Référence des Maladies Auto
157 Inflammatoires rares et des Amyloses/National reference center for autoinflammatory diseases
158 and inflammatory amyloidosis) and the CEREDIH (Centre de Référence des Déficits
159 Immunitaires Héritaires). Their medical records were retrieved for analysis.

160
161 “Non-specific agammaglobulinemia and hypogammaglobulinemia” terms designed
162 predominantly antibody deficiency (PAD) patients who did not fulfill criteria for CVID nor X-
163 linked and are defined by a decrease in IgG and IgA/IgM below 2 SD. CVID corresponds to a
164 more stringent definition (ESID definition) including poor antibody response to vaccines (and/or
165 absent isohemagglutinins) and/or defects in switched memory B cells (11), the definition of
166 CVID was used only when comprehensive data were available. Hence, some patients with
167 hypogammaglobulinemia/ non-specific agammaglobulinemia may correspond to CVID patients.
168 We separated the cases of PID complicated by AAA in 3 different groups: all cases of PID

169 combined; cases affected by the most frequent PID, CVID, and cases affected by the most
170 frequent type of PID, humoral deficiency (12).

171

172 Finally, we analyzed the 2 new cases from CEREMAIA and 35 articles from the systematic
173 literature review (8,9,13–46). Descriptive statistics were performed using the excel software.
174 (Figure 1)

175

176

177 **Results**

178 ***Description of the two new French cases***

179 *Case 1:* A 26-year-old patient from consanguineous parents was addressed in 2016 for weight
180 loss, fever, diarrhea, ascites, dyspnea, and cough evolving for a few months. Two of his brothers
181 had died before 30 years old years. His medical history revealed CVID with B-cell lymphopenia
182 with absent switched memory B cells, which had not been treated with immunoglobulin
183 replacement therapy (IRT). His serum C-reactive protein (CRP) was elevated during infections,
184 and normalized in-between. The clinical examination revealed lymphadenopathy, clubbing
185 (Figure 2 A), edema, and signs of respiratory failure. CT scan showed cystic bronchiectasis
186 (Figure 2 B) and an irregular, excavated opacity with an air-fluid level associated with pleuritis
187 and ascites. During a hospitalization for pulmonary infection, a nephrotic syndrome was detected
188 with normal renal function. Laboratory exams showed normal total cells count except for
189 lymphocytosis at 7.22 g/l, CRP at 23 mg/l, and total immunoglobulin (Ig) level of 0.6 g/L (IgG
190 3.09 g/L, IgA <0.063 g/l and IgM 0.26 g/l). Lymphocyte immunophenotyping revealed B-cell
191 lymphopenia without autoantibodies. A salivary gland biopsy showed abundant amyloid deposits
192 staining with AA-antibody (Figure 2 C) confirming the diagnosis of AAA. No *MEFV* mutation
193 was detected by Sanger sequencing. The patient was discharged with long-term roxithromycin
194 treatment to prevent pulmonary infection, and IRT was started. Unfortunately, he died at 29 years
195 from sepsis and acute respiratory failure.

196 *Case 2:* A woman was diagnosed with CVID at the age of 20 years because of recurrent severe
197 respiratory tract infections, bronchiectasis, and severe hypogammaglobulinemia. Immunological
198 studies demonstrated absence of IgG and IgA with very low IgM level (0.13 g/l), lymphopenia
199 with marked CD4 lymphopenia (144/mm³), Between the age of 35 years and 58 years, she
200 received intermittent intramuscular IRT, then continuous intravenous IRT, and finally
201 subcutaneous IRT. Antibiotic prophylaxis with azithromycin and trimethoprim/sulfamethoxazole
202 was added because of persistent infections including pneumonia and other respiratory tract
203 infections, but also HPV, VZV, and HSV infections and Norovirus infection. At the age of 68
204 years, she was admitted for diarrhea, weight loss, and severe portal hypertension, renal
205 dysfunction, and microalbuminuria. A kidney biopsy and revealed tubular and vascular AA
206 protein deposits. Genetic studies identified two compound heterozygous *LRBA* variants (*Exon 57*
207 *c.8426 C>T* and *c.8464 G>A*). The first variant (*c.8426 C>T*; p.S2809L) is a very frequent SNP

208 found at 2.10-1 in GNOMAD public database. She died at 73 years old from complications of
209 portal hypertension.

210 *Literature review*

211 *Main features of PID associated with AAA*

212 While various immune deficiencies and mechanisms of PID were found, antibody deficiencies
213 were the most frequent type of PID associated with AAA. CVID (n=14) and non-specific
214 agamma- and hypogammaglobulinemia (n=12) were predominant, followed by X-linked
215 agammaglobulinemia (XLA) (n=4), chronic granulomatous disease (CGD) (n=3), Hyper IgM
216 syndrome (n=3), hereditary complete C4 deficiency (n=1), Leucocyte Adhesion Deficiency
217 Type-1 (n =1), Hyper IgE syndrome (n=1), and Chediak-Higashi syndrome (n=1) (Figure 3).
218 While 8 patients had “infections only” CVID, 6 had CVID associated with other complications
219 such as autoimmune disease, granulomatous disease and lymphocytic infiltration.

220 We studied AAA-associated PID in three different groups: first in all PID combined and then in
221 two specific groups according to the IUIS classification (1):CVID group and predominantly
222 antibody deficiency (PAD) group. In our review, CVID, non-specific agamma- and
223 hypogammaglobulinemia, and X-linked agammaglobulinemia were classified as PAD according
224 to the IUIS. Global sex ratio was 1.7. The mean age at first signs of immune deficiency was
225 17.25 years in all PID combined group, 18.5 years in the CVID group, and 20.75 years in the
226 PAD group. A diagnostic delay of 10.39 +/- 7.04 years was noted in all PID combined group,
227 with 4 additional years in the CVID group. (Table 1)

228 Consanguinity was identified in 9 patients. Family history was compatible with PID in 12
229 patients. Genetic analysis was performed in 6 cases (9,35,38,40 and case 2). One homozygous
230 mutation was identified in exon 12 of *ITGB2* (C590R/C590R) (36), leading to a diagnosis of
231 Leukocyte Adhesion Deficiency Type-1 (47). Two heterozygous non-synonymous amino acid
232 substitutions in the *NLRP12* gene, encoding the NALP12 protein (p.H304Y and p.A629D) (41);
233 and our case 2 with two heterozygous compound missense variants of *LRBA*.

234 PID was associated with lymphoproliferation (lymphadenopathy or splenomegaly n=8), hepatic
235 complications (regenerative nodular hyperplasia and lymphoid infiltration n=1, hepatomegaly
236 n=1), dermatological manifestations (oral and perianal ulcerations n=1, psoriasis n=1), clubbing
237 (n=6), growth retardation (n=5), non-infectious arthritis (n=3), adrenal insufficiency (n=2),

238 anemia (n=2), cardiac features (n=1), partial albinism/ataxia/mental deficiency (n=1), and seizure
239 (n=1). “Infections only” CVID represented 57% of the CVID group. The sites and types of
240 infection were extremely varied and were mainly bacterial with pulmonary involvement, but
241 viral, parasitic, and fungal infections were also reported. Twenty-one patients had bronchiectasis
242 (52,5%). Eight patients had tuberculosis.

243 Treatments were mostly intended to prevent infections: IRT (n=26) given intravenously or
244 intramuscularly, prophylactic antimicrobial therapy (trimethoprim n=2, co-trimoxazole n=1,
245 levofloxacin/roxithromycine n=1, azithromycin n=1, penicillamine and itraconazole n=1, and
246 undefined n=1), intravenous white blood cell transfusion (n=1), and interferon- γ (n=1). A
247 minority of treatment were directed against the PID itself: abatacept (n=1), omalizumab (n=1),
248 and corticosteroids (n=1). Delay between first symptoms of PID and onset of treatment was 12.41
249 +/-7.58 years. Three patients were not compliant with treatment. (Table E1)

250

251 *Main features of PID-associated AAA (Figure 4)*

252 The mean age at diagnosis of AAA was 33.41 +/- 18.15 years in all PID combined group, ranging
253 from 5 to 75 years. On average, CVID and PAD were diagnosed 4 years later. The average delay
254 between first symptoms of PID and AAA diagnosis was 16.17 +/- 7.08 years in all PID combined
255 group, like the CVID and PAD groups. Concomitant diagnosis of PID and AAA was made in 13
256 patients.

257 The most common presentation of AAA was renal involvement, with nephrotic syndrome in the
258 majority (n=21), non-nephrotic proteinuria (n=10), and renal failure (n=6). Other clinical
259 manifestations involved gastro-intestinal signs and symptoms (mostly diarrhea, hepatic
260 involvement, and splenomegaly), deterioration of general state, adrenal insufficiency, heart
261 failure, and goiter. Histological diagnosis was made in 10 autopsies, mostly in the oldest cases
262 reported. Renal tissue was most commonly analyzed (n=20), followed by the intestinal tract
263 (n=13), node and spleen (n=10), liver (n=4), lungs (n=3), abdominal fat (n=1), thyroid (n=3),
264 adrenal glands (n=3), skin (n=1), heart (n=1), and salivary glands (n = 1).

265 In patients who received therapy directed against AAA, 6 were given colchicine, 2 steroids, 1
266 tocilizumab, 1 infliximab, 1 omalizumab, and 1 abatacept. Two patients underwent hemodialysis,
267 and none were transplanted. (Table E2).

268 **Discussion**

269 AAA is a rare complication of PID (48). Available data is scarce, relying on case reports and,
270 until more recently, on autopsies. Morbidity reviews and studies on PID usually do not mention
271 AAA (49,50). With only 40 cases reported in more than 60 years and none reported in large case
272 series, this work confirms the existence and rarity of AAA occurrence in the PID course (51–55).
273 The typical clinical picture is a patient displaying recurrent infections, mostly bacterial
274 pneumonia, since adolescence or beginning of adulthood, with a delayed diagnosis of PID and
275 onset of treatment after 10 years of evolution. The course is marked by chronic pulmonary
276 infections as illustrated by bronchiectasis for more than half of them, eventually leading to
277 development of a nephrotic syndrome revealing AAA 16 years later (figure 4). AAA is
278 associated with a poor prognosis in PID: 22 out of 40 patients, died during follow-up, at an
279 average age of 36.1 years old.

280
281 Antibody disorders, especially CVID and non-specified agamma- and hypogammaglobulinemia,
282 are the predominant PID complicated by AAA, which parallels their prevalence in national
283 registers (53,56–59). Thus, for AAA to complicate PID, the latter must be severe enough to
284 develop chronic infections, but mild enough to allow a prolonged course of chronic
285 inflammation. A possible additional explanation for overrepresentation of PAD in our study is the
286 fact that patients with primary antibody defects are rarely undergoing hematopoietic stem cell
287 transplantation (HSCT), as Ig supplementation is usually sufficient to avoid life-threatening
288 complications. As AAA is linked to a persistent activation of innate immune cells resulting in a
289 chronic biological inflammatory syndrome, HSCT might be involved in direct protection against
290 amyloidosis. AAA risk might therefore be underevaluated in patients with early-onset PIDs
291 hampering innate or non B cell adaptative immunity and leading to an early consideration for
292 HSCT. However it is a complication that can develop rapidly in certain contexts, as illustrated by
293 the case of a pediatric diagnostic LAD-1 that developed amyloidosis at the age of 11 years old.
294 Moreover, 32,5% of PID diagnosis were made when AAA was diagnosed. From the clinical point
295 of view, it suggests the value of looking for PID in the etiologic search for AAA.

296 The late PID diagnoses (51–55,60) and length of diagnostic delays (11,60–62) are partly due to
297 older publications (12,61–63) as well as the numerous cases of CVID which are known to have

298 longer diagnostic delays. but it also may have promoted chronic inflammation for AAA. In CVID
299 complicated by AAA, the first symptoms appeared rather early in life compared to non-AAA
300 CVID (5,51,62,64–66), thus suggesting an underlying genetic defect. Moreover, despite having a
301 generally better prognosis (49,67) “infections only” CVID was more often complicated by AAA
302 than CVID presenting other non-infectious complications (49,67) highlighting a potential
303 contributing role of infections in AAA secondary to CVID.

304
305 Bronchiectasis was overrepresented (52,5%) (52,56,62,68). The specific association between
306 antibody deficiencies and bronchiectasis as already been reported (69). Bronchiectasis was
307 present in 90% of our CVID group, compared to 23% in Gathman’s series (51), 37% in
308 Oksenhendler’s series, and 51% in Ramirez-Vargas’s series (68). Thus, bronchiectasis in PID
309 could be used as a warning sign of chronic inflammation and increased risk of developing AAA.
310 In the absence of prior PID diagnosis, diagnosis of bronchiectasis among patients with AAA
311 diagnosis must lead to PID screening, particularly antibody deficiencies.

312
313 PID patients with AAA share some similarities with other patients developing AAA: the renal
314 involvement is the main symptomatic sign of AAA (48), the duration between the underlying
315 disease onset and AAA diagnosis is similar to the mean delay all underlying disorders combined
316 for AAA occurrence (6) and to the one reported in other immune dysregulation disease such as
317 inflammatory bowel disease (70) and rheumatoid arthritis (71). However, some chronic infections
318 such as tuberculosis (72) have a much shorter delay whereas it is slightly longer for the hereditary
319 periodic fever syndromes (73). AAA seems to develop earlier in life in PID (6,74) than in other
320 inflammatory diseases, which may be partly explained by the early onset of PID. Even if data for
321 a prevalence evaluation of AAA in PID were not available because AAA is a very rare
322 complication of PID as explained above, this prevalence correlates with the underlying disease .
323 AAA is more common in monogenic periodic fever syndromes such as Familial Mediterranean
324 Fever (75).

325
326 This study raises the question of therapeutic issues in the management of PID complicated by
327 AAA. Once the underlying PID is diagnosed and, if possible, treated, the first step should be to

328 optimize control of chronic inflammation caused by recurrent infections, with the possibility of
329 inducing AAA regression (76). Although new protocol for Primary Immune Regulatory
330 Disorders have been developed, to examine HSCT and other treatment for this group of disorders
331 (77), in such population, we believe that immunomodulatory agents such as anti-IL1 or anti-IL6
332 immunotherapies should be preferred as in other patients with AA amyloidosis without
333 underlying immune defects. These agents increase the risk of severe bacterial events but this risk
334 seems lesser than the treatment related toxicities of HSCT. Moreover, this risk can be
335 circumscribed by Ig supplementation and antibioprohylaxis. In other PID situations,
336 amyloidosis discovery could prompt to discuss early HSCT.

337 The occurrence of AAA in PID is low, suggesting that infections may not be the only
338 predisposing factor for this complication. IBD and enteropathies are common in CVID, CGD,
339 Leucocyte Adhesion Deficiency and could increase the risk of AAA in PID patients and one case
340 of enteropathy (case 2) was reported but unfortunately, the available data was insufficient to
341 provide a prevalence of IBD for patients with AAA secondary to PID. Many cases were reported
342 before advances in genetics; given the high percentage of PID patients with consanguinity and
343 culprit mutations identified since 2011, all PID patients developing AAA could get deep genetic
344 analysis in order to identify underlying genetic defects and corresponding pathophysiological
345 mechanisms that could have promotes chronic inflammation and trigger AAA. Going forward,
346 the next step will be using next generation sequencing to determine if certain genotypes are
347 particularly associated with AAA occurrence in PID patients.

348
349 Finally, as a national reference center for AAA in an industrialized country, following the
350 occurrence of 2 such cases within 1 year,, it appeared important for us to point this complication
351 out to other specialists given the simplicity of non-invasive screening (proteinuria and renal
352 function monitoring) versus the life threatening consequence of AAA. Because of the high
353 prevalence of bronchiectasis in AAA associated to PID we propose to systematically look for
354 hypogammaglobulinemia in AAA with no other cause than bronchiectasis and the realization of a
355 thoracic imaging in the AAA check-up to detect bronchiectasis. In order to prevent and detect
356 earlier the occurrence of AAA: we recommend for patients with PID the realization of an annual
357 proteinuria/creatininuria ratio and a biannual plasma creatinine and CRP assays in the absence of
358 acute infectious complications. This assessment seems to us to be sufficient, the digestive signs

359 of AAA being rather non-specific in particular diarrhea and the cardiac involvement being very
360 rare in AAA unlike other amyloidosis such as AL amyloidosis and ATTR amyloidosis. In the
361 future, a prospective study for proteinuria/creatininuria on a large cohort of PID and, depending
362 on the results, a biopsy of the accessory salivary glands, which would be minimally invasive,
363 could be interesting in order to evaluate this association and its incidence.

364

365 **Conclusion**

366 AAA is a long-term life-threatening complication of PID portending a poor prognosis. Despite
367 improved understanding of PID, earlier diagnosis, and the availability of therapies for infection
368 prevention and control, PID remain severe and potentially lethal diseases. This work emphasizes
369 the importance of prompt identification of PID symptoms by general practitioners, pediatricians,
370 and other specialists. Once a correct diagnosis is established, institution of measures to prevent
371 infection (vaccination, IRT, and prophylactic antimicrobial therapy if needed) can play a key role
372 in avoiding such complications.

373

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562 **Table's legends**

563 **Table 1 Epidemiological data of PID complicated by AAA**

564 **Abbreviations;** AAA AA Amyloidosis; PID Primitive Immunodeficiency; Yrs Years; CVID
565 Common variable immunodeficiency

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567 **Figure's legends**

568 **Figure 1. Flow-chart diagram depicting the selection process**

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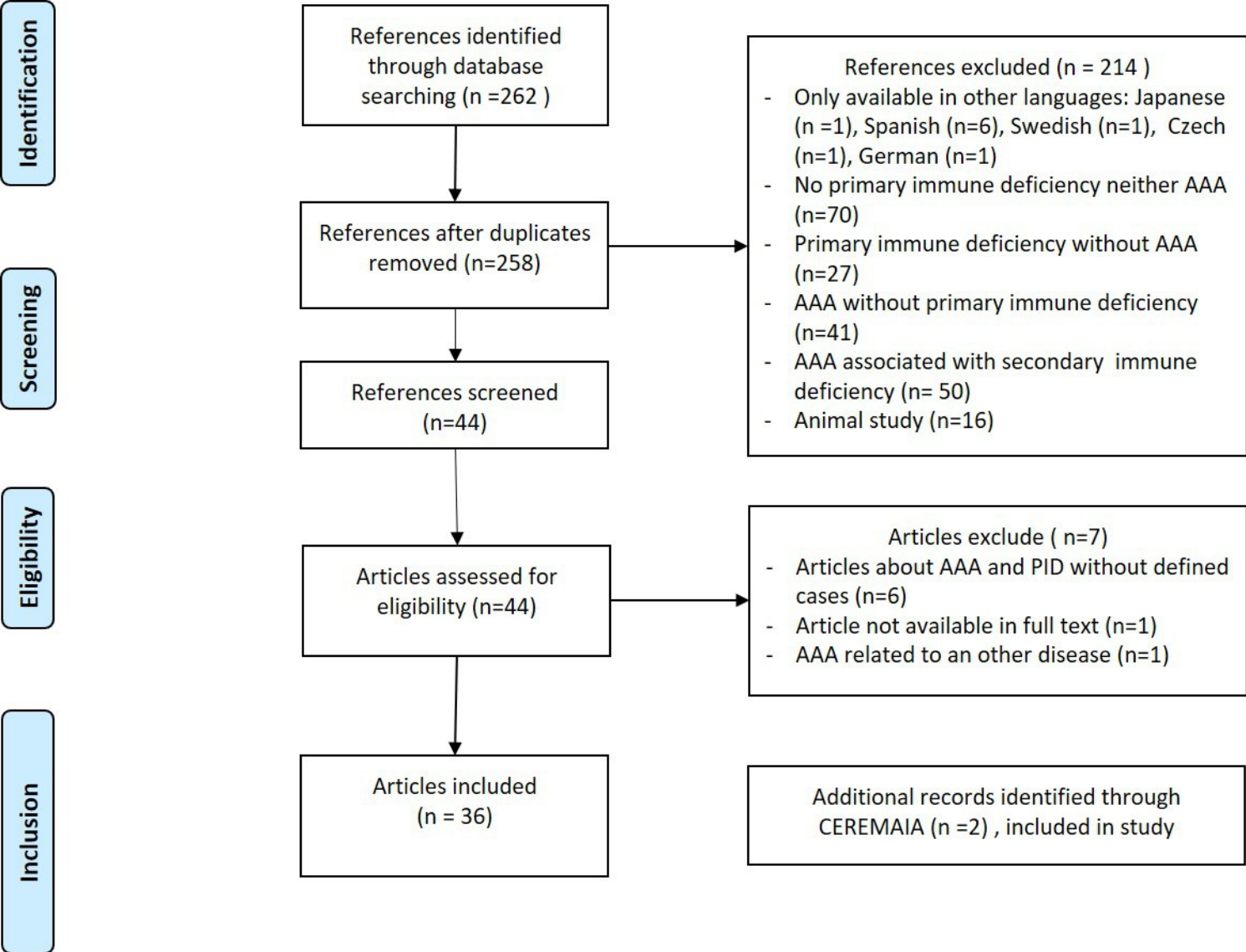
572 **Figure 2. Case 1**

573 **A. Clubbing B. CT Chest: Diffuse bronchiectasis C. Microscopic feature of salivary biopsy**
574 **showing amyloid deposition around the salivary ducts (C.1 Congo red stain, × 100 and**
575 **C.2 Immunohistochemical reactivity of deposited material with anti-amyloid A protein x400**

576 **Figure 3. Distribution of included patients into the 9 major diagnostic categories of PID (1)**

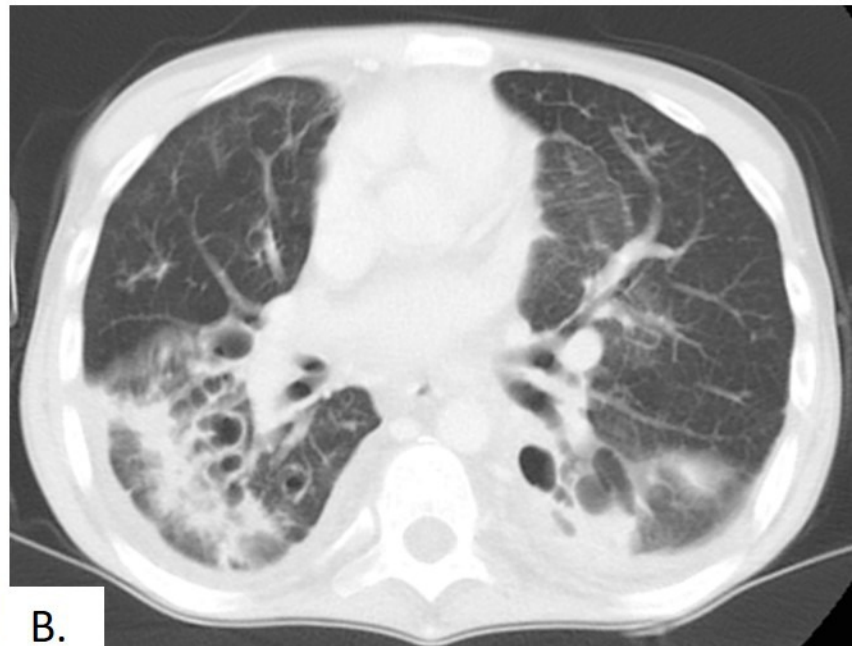
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578 **Figure 4 Synthesis of the natural history of AAA in PID**

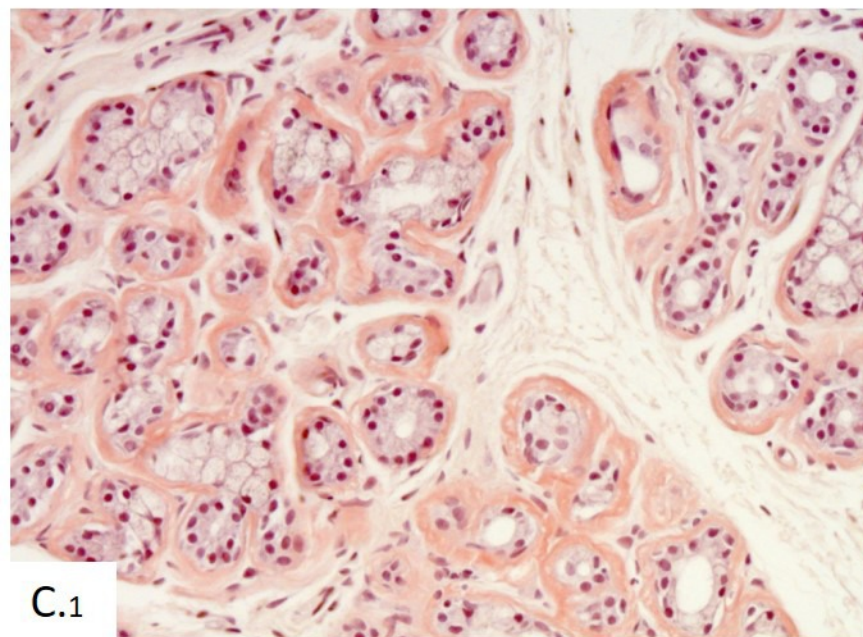




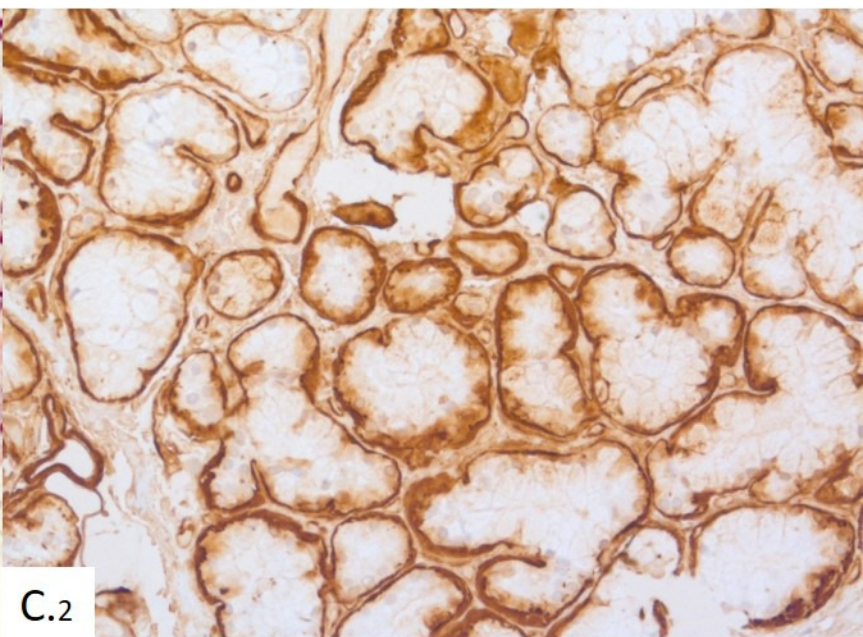
A.



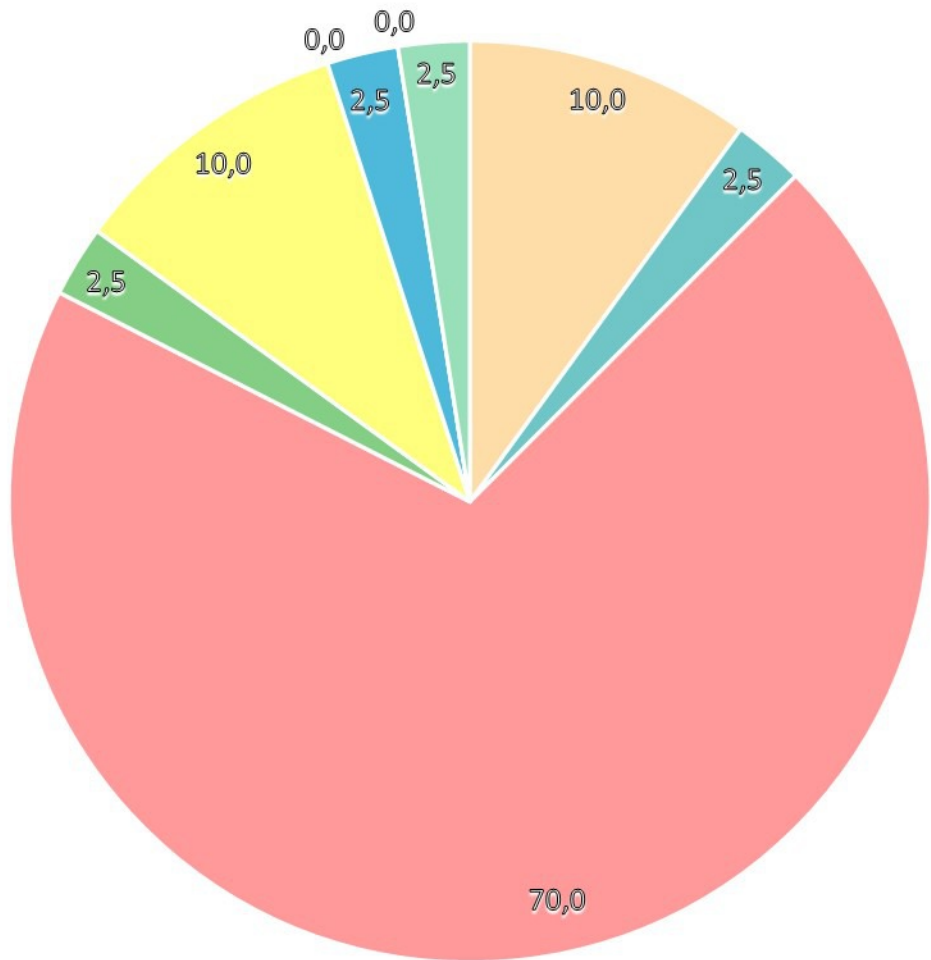
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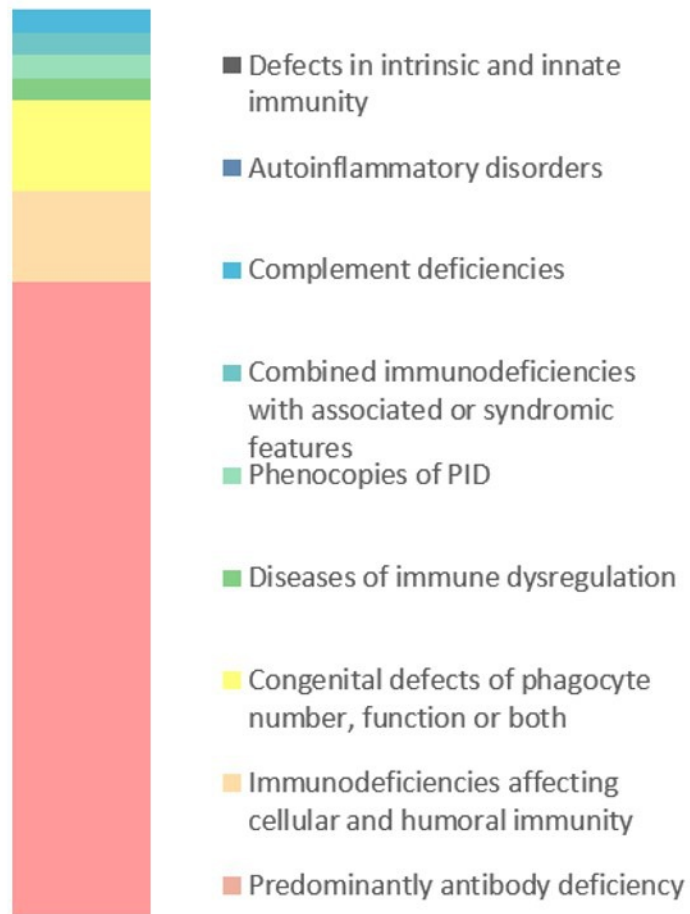
C.1



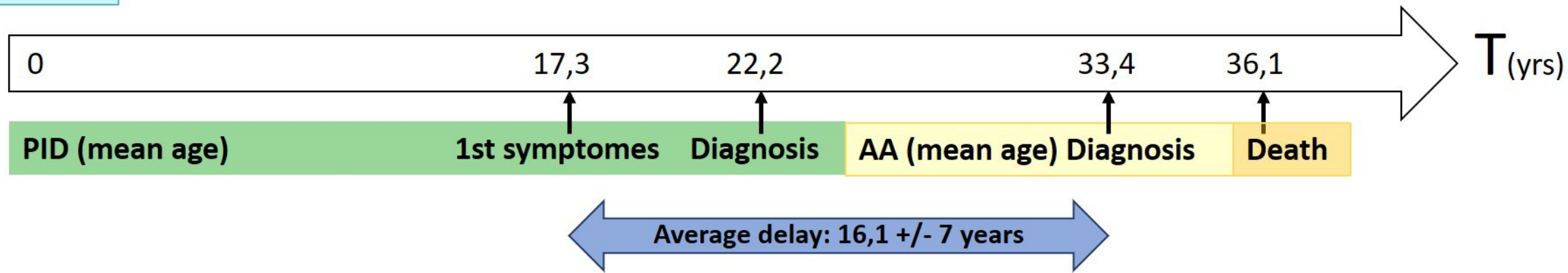
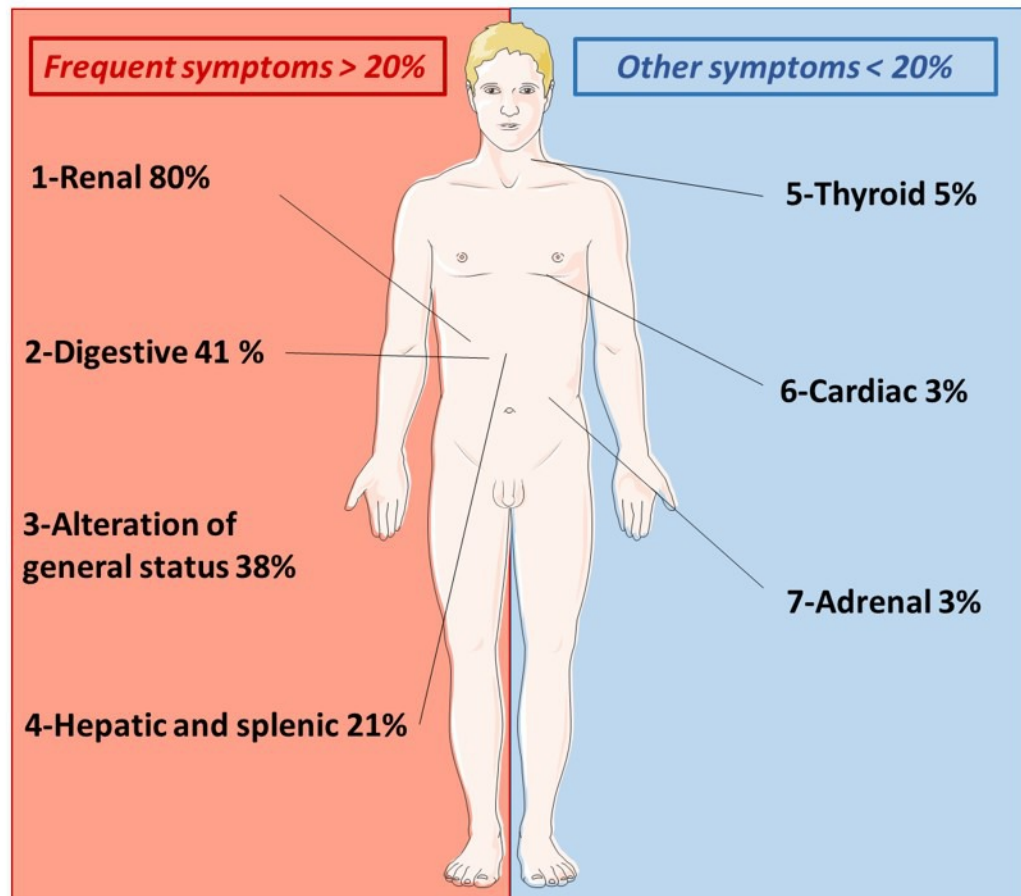
C.2



- Immunodeficiencies affecting cellular and humoral immunity
- Combined immunodeficiencies with associated or syndromic features
- Predominantly antibody deficiency
- Diseases of immune dysregulation
- Congenital defects of phagocyte number, function, or both
- Defects in Intrinsic and Innate Immunity
- Complement deficiencies
- Autoinflammatory disorders
- Phenocopies of PID



Consanguinity
22,5%



	Mean age (yrs)			Minimum age (yrs)			Maximum age (yrs)			Standard deviation (yrs)		
	All PID	CVID	PAD	All PID	CVID	PAD	All PID	CVID	PAD	All PID	CVID	PAD
First signs of PID	17.25	18.50	20.75	0	7	0	64	64	64	17.98	18.86	17.91
Diagnosis of PID	22.20	28.86	25.64	0.17	9.00	0.17	64	64	64	16.02	14.75	15.99
Initiation of treatment of PID	27.06	33.00	31.19	0.17	24.00	0.17	74	48	74	20.33	7.71	17.67
First signs of AAA	32.41	38.14	38.26	7	20	12	72	72	72	17.32	16.83	16.23
Diagnosis of AAA	33.41	39.03	39.13	7	20.5	12	75	75	68	18.15	17.34	16.77
Death	36.13	41.00	41.88	8.5	21	15	75	73	75	20.27	20.49	18.41
Delay between first signs of PID and AAA diagnosis	16.17	16.14	16.82	2	2	2	29	22	29	7.08	6.94	7.41
Delay between first signs of PID and PID diagnosis	10.39	14.00	11.12	0	0	0	22	22	22	7.04	7.95	7.35
Delay between first signs of PID and initiation of treatment	12.41	20.67	13.90	0	0	0	22	22	22	7.58	1.54	7.43