



HAL
open science

Acute Myeloid Leukaemia following Direct Acting Antiviral drugs in HCV-infected patients: a 10 years' retrospective single-center study

Carole Scheifer, Elena Luckina, Bénédicte Lebrun-Vignes, Abdoul-Aziz Diop, Dominique Damais-Thabut, Damien Roos-Weil, Agnès Dechartres, Pascal Lebray

► To cite this version:

Carole Scheifer, Elena Luckina, Bénédicte Lebrun-Vignes, Abdoul-Aziz Diop, Dominique Damais-Thabut, et al.. Acute Myeloid Leukaemia following Direct Acting Antiviral drugs in HCV-infected patients: a 10 years' retrospective single-center study. *Clinics and Research in Hepatology and Gastroenterology*, 2022, 46 (8), pp.102000. 10.1016/j.clinre.2022.102000 . inserm-03868217

HAL Id: inserm-03868217

<https://inserm.hal.science/inserm-03868217>

Submitted on 23 Nov 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

1 **Acute Myeloid Leukaemia following Direct Acting Antiviral drugs**
2 **in HCV-infected patients: a 10 years' retrospective single-center**
3 **study**

4
5
6 Scheifer Carole¹, Luckina Elena², Lebrun-Vignes Bénédicte^{2,3}, Diop Abdoul-Aziz⁴, Damais-
7 Thabut Dominique⁶, Damien Roos Weil¹, Dechartres Agnès⁵, Lebray Pascal⁶

8 1- Sorbonne Université, Département d'Hématologie clinique, Assistance Publique Hôpitaux de Paris, Hospital Pitié-Salpêtrière, Paris, France
9 2- Sorbonne Université, Centre Régional de Pharmacovigilance, Assistance Publique Hôpitaux de Paris, Hospital Pitié-Salpêtrière, Paris,
10 France
11 3 - EpiDermE, Univ Paris Est Créteil, Créteil, France.
12 4- Sorbonne Université, Département d'information médicale, Assistance Publique Hôpitaux de Paris, Hospital Pitié-Salpêtrière, Paris, France
13 5- Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique, AP-HP.Sorbonne Université, Département de
14 Santé Publique, Centre de Pharmacoépidémiologie (Cephepi), Paris, France
15 6 Sorbonne Université, Département d'hépatogastroentérologie, Assistance Publique Hôpitaux de Paris, Hospital Pitié-Salpêtrière, Paris,
16 France

17
18
19
20 **Corresponding author:**

21 Carole Scheifer, Département d'Hématologie clinique, Assistance Publique Hôpitaux de Paris,
22 Hospital Pitié-Salpêtrière, Paris, France

23 Mail: carole.scheifer@aphp.fr

24 **Number of words:**

25 Abstract Words: 357

26 Main text Words: 3632 (including figures and tables)

27

28

29

30

31
32 **ABSTRACT**

33 *Background*

34 After several cases of peculiar hematological malignancies following introduction of new oral
35 anti-hepatitis C virus (HCV) treatments in our recent practice, we aimed to systematically
36 identify all cases of hematological malignancies (HM) in patients with chronic HCV infection
37 and to compare them according to the prescription of oral anti-HCV Direct Acting Antivirals
38 (DAA) treatment or not.

39 *Material/methods:*

40 In this single-center retrospective observational study, we included all patients with confirmed
41 HM and chronic HCV infection managed between 2010 and 2019 in the Pitié-Salpêtrière
42 hospital, Paris. Non-inclusion criteria were a benign hematological disorder, an HM preceding
43 chronic HCV infection and HCV acute infection. We compared characteristics of patients who
44 received DAA before HM diagnosis to those with no DAA before HM.

45 *Results:* Over the 10 years, 61 cases of HM among HCV infected patients were identified
46 (female 29%, median age of 58.0 years [IQR 17]). Twenty-one received DAA before the onset
47 of HM (Group DAA+) and 40 did not (Group DAA-) including 22 having received DAA after
48 HM. In the DAA+ group, oral NS5B, NS5A and NS3A inhibitors were used in 90, 76 and 29%
49 respectively. HM developed in the two years following DAA initiation in 76%. Eight (38%)

50 had Non-Hodgkin Lymphoma, 5 (24%) had an Acute Myeloid Leukaemia (AML) including
51 two with a mixed phenotype, 2 each had Hodgkin Lymphoma, Multiple Myeloma or a
52 myeloproliferative disorder and one each had a chronic Lymphocytic Leukaemia or AL
53 Amyloidosis. In the Group DAA–, HM were NHL in 20(50%) patients, Myeloproliferative
54 neoplasms in 7 (17%) , Multiple Myeloma in 5, Hodgkin Lymphoma in 3, Myelodysplastic
55 syndrome and AML in 2 (5%) each and Acute Lymphoblastic Leukaemia in one. No
56 significant difference between the groups DAA + and – was found according to age, sex, HCV
57 genotype, viral load, co-infection or type and exposition of previous HCV treatments. AML,
58 liver transplantation and cirrhosis were significantly more frequent in the DAA+ group (p =
59 0.020, 0.045 and 0.032, respectively).

60 ***Conclusion***

61 AML seemed more frequent after using DAA treatments, notably in severe HCV patients
62 including cirrhotic and/or liver transplanted patients. A multicentric observational study is
63 ongoing to confirm and explore the results.

64

65 **KEYWORDS**

66 Hepatitis C virus

67 Hematological malignancies

68 Direct Acting Antivirals

69 Acute Myeloid Leukaemia

70 Mixed-phenotype Acute Leukaemia

71

72

73

74 **INTRODUCTION**

75 Chronic hepatitis C virus infection (HCV) remains a global public health concern affecting an
76 estimated 71.1 million (62.5–79.4) individuals worldwide with mortality four times higher
77 compared to general population (1-3).

78 The interferon-free direct antiviral agents (DAA), first used in 2011, have been a major
79 milestone in the HCV infection treatment due to their efficacy including on severe cirrhosis or
80 liver transplantation and their few side effects (4). Since 2016, the World Health Organization
81 recommends DAA as a first-line treatment without interferon for every chronic HCV infection
82 (5). DAA related viral eradication may result in a decreased risk of HCV related B-cell
83 lymphoma and possible regression of HCV related Non-Hodgkin Lymphoma (NHL) (6, 7).

84 However, several studies have suggested an increased early occurrence or recurrence of
85 hepatocellular carcinoma after DAA use, raising concerns about safety and oncogenicity (8, 9).

86 Nonetheless, these new insights have not been confirmed by other studies including meta-
87 analyses (10). Even though HCV infection and liver transplantation are known risk factors for
88 hematological malignancies (HM), predominantly of the B-cell type (4, 11, 12), some recent
89 case studies suggest a possible increase in hematological disorders secondarily to DAA
90 administration (13-17), which is consistent with our own experience.

91 This retrospective study aimed to identify and describe all cases of hematological malignancies
92 (HM) in patients with chronic HCV infection in hematology or hepatology units in our hospital

- 93 and to compare characteristics of patients according to the prescription of oral anti-HCV Direct
- 94 Acting Antivirals (DAA) treatment or not.

95 **MATERIALS AND METHODS**

96 **STUDY DESIGN AND SETTING**

97 This is a single-center retrospective observational study.

98 **IDENTIFICATION OF RELEVANT PATIENTS**

99 Every adult patient with a HM and a chronic hepatitis C infection managed between
100 01/01/2010 and 28/03/2019 in the hematology and/or hepatology departments of the Pitié-
101 Salpêtrière hospital, in Paris, France was eligible. HM were defined according to WHO
102 classifications. Chronic HCV infection was defined as an infection lasting for at least 6 months
103 according to the hospital chart with at least one available HCV viral load. Patients were
104 identified through the list of in- and outpatients managed in the hematology or in the
105 hepatology departments. Non-inclusion criteria were HCV acute infection, benign
106 hematological disorder and HM preceding HCV. In patients with a first HM, a minimal period
107 of remission of 1 year before DAA administration was necessary to get included. Patients with
108 a diagnosis of HM < 3 months following DAA initiation were also excluded. This arbitrarily
109 limits the risk of including a patient with relapsing or subclinical HM at the initiation of DAA.
110 The retrospective analysis of anonymized data is allowed by French law and all the patients
111 during their medical care were informed of their right to refuse that their data may be used for
112 research purpose. Our study was locally registered according to the General Data Protection

113 Regulation. All cases with a HM after a treatment using DAA were declared to the local
114 pharmacovigilance centre.

115 We evaluated whether eligible patients had received DAA and if so, we recorded the date of
116 dispensation from the database provided by the Pitié-Salpêtrière pharmacy department.

117 Eligible patients were classified in 2 groups according to the sequence between DAA treatment
118 and HM: Group DAA+ included patients who initiated their first DAA at least 3 months before
119 HM diagnosis. Group DAA- included patients with no DAA before HM.

120 DATA EXTRACTION

121 The following detailed information was retrospectively collected from the medical charts of
122 each patient:

123 - Socio-demographic data including sex and age

124 - Characteristics of the HCV infection: genotype, viral load at time of MH diagnosis, HIV or
125 HBV co-infection, severity of liver disease according to the combination of noninvasive tests
126 (Fibroscan[®] and/or Fibrotest[®]) or to a liver biopsy, hepatocellular carcinoma diagnosis.

127 - Date of liver transplantation if applicable

128 - Past HCV treatments including interferon, pegylated interferon or ribavirin use, with date and
129 duration for each and DAA treatments with the type of combo drugs (NS5B, NS5A and NS3A
130 inhibitors).

131 - Risk factors for malignant hemopathy: hematological disease at risk, past exposure to chemo-
132 or radiotherapy, AIDS, solid organ transplantation or other immunosuppression.

133 - Hematological malignancy: type, date of diagnosis, time between the first administration of
134 DAA and occurrence of the HM, duration of follow up after HM diagnosis, treatment including
135 bone marrow transplantation, outcome (survival or death).

136 STATISTICAL ANALYSES

137 We compared baseline characteristics, types of HM and outcomes in consecutive HCV patients
138 with a HM diagnosis according to previous DAA therapy or not. As the hepatology unit
139 proposed many anti-HCV DAA protocols since 2011 and the patients could have been treated
140 with two or more DAA lines, we decided not to make a comparison by periods to limit the risk
141 of an analytic bias.

142

143 STATISTICAL METHODS

144 All statistical analyses were done using RStudio Version 1.0.153. (R Core Team (2020). Patient
145 characteristics were described as numbers and percentages for categorical data and as medians
146 with interquartile range (IQR) for quantitative variables. Quantitative variables were compared
147 using the Wilcoxon-Mann-Whitney test; qualitative variables were compared by the Chi2 test
148 or the Fisher's exact test as appropriate. Survival times since diagnosis of HM were compared

149 between groups DAA+ and DAA- using a Kaplan Meier curve and Cox test. A *p*-value < 0.05
150 was considered statistically significant. Cut-off date for data collection was 23/12/2020.

151

152 **RESULTS**

153 **SELECTION PROCESS**

154 From the 15,842 patients managed in the hematology department and the 3,499 patients

155 managed in the hepatology department between 01/01/2010 to 28/03/2019, we identified 164

156 potentially eligible patients. From these, 103 patients were excluded mainly for a benign

157 hematological disorder (n = 49), or the absence of chronic HCV infection (n = 22) (Figure 1

158 and Supplemental data 1). Finally, 61 patients had a history of HM and chronic VHC infection

159 and were included in this study. All but four were followed in the hematology department of

160 our hospital.

161 Twenty-one patients had a history of DAA use before HM diagnosis and were included in the

162 DAA+ group. The DAA- group comprised 40 patients, having a history of chronic HCV

163 infection without any DAA prior to HM diagnosis with 18 patients that never received any

164 DAA and 22 having received DAA following HM diagnosis. Detailed information can be

165 found in Table 1.

166 **PATIENT CHARACTERISTICS**

167 Among the 61 HCV positive patients identified with HM, 29% were female with a median age
168 at diagnosis of HM of 58 years [IQR 17]. HCV genotype 1 represented 60% of the cohort.
169 Nine patients had an HIV infection, 2 an HBV co-infection. There was no significant difference
170 between DAA + and DAA- groups, including age, sex, HCV genotype or viral load, co-
171 infection, ALT levels, F Metavir stage at baseline, except for history of cirrhosis and liver
172 transplantation which were significantly more frequent in the DAA+ group (52% vs. 30%, $p =$
173 0.032 and 38% vs. 12.5%, $p = 0.045$, respectively).

174 ANTI-HCV TREATMENTS

175 Type of previous anti-HCV treatments is detailed in Table 1. Groups were not significantly
176 different in type and exposition of first line anti-HCV treatments with interferon and/or
177 ribavirin. Five of 21 patients in the DAA+ group received at least 2 DAA treatment lines with
178 the first line combining DAA with ribavirin ($n = 2$) or ribavirin + interferon ($n = 3$).
179 NS5B, NS5A and NS3A inhibitors were part of the last all oral DAA combo treatments in 90,
180 76 and 29% respectively (Supplemental data 2). Median exposition time to DAA was 3 months
181 [IQR 3]. Median time between initiation of DAA and HM diagnosis was 16.5 months [IQR
182 20.5] with all HM diagnosed within 6 years after DAA exposure including 3/4 in the first 2
183 years following DAA initiation.

184 TYPE OF HEMATOLOGICAL MALIGNANCIES

185 Of the 21 patients in the DAA + group, 8 (38%) had a NHL, including 4 EBV induced Post
186 Transplantation Lymphoproliferative Disease, vs. 20 NHL (50%) in the DAA- group ($p =$
187 0.42). Surprisingly, 5 (24%) patients in the DAA+ group had acute myeloid Leukaemia (AML)
188 vs. only 2 (5%) in the DAA- group, with a significant difference ($p = 0.02$). While both DAA-
189 patients with AML had previous HM known as risk factor, 3 of 5 DAA+ patients with AML
190 had no specific risk factor including 2 with a Mixed-phenotype Acute Leukaemia (MPAL), a
191 rare and poor-prognosis Leukaemia. Finally, 4 of the 5 DAA+ AML patients developed their
192 HM in the first 3 years following successful DAA combo therapy. All five received a NS5B
193 inhibitor (sofosbuvir). One of the 2 patients with mixed-phenotype acute Leukaemia had the
194 highest number of DAA treatment lines (3) and the largest total duration of sofosbuvir (9
195 months).

196 RISK FACTORS FOR HEMATOLOGICAL MALIGNANCIES

197 In the DAA+ group, only 2 of the 21 cases were associated with a delayed recurrence of a NHL
198 at 4 years and a multiple myeloma at eight years. Among the 19 patients with first onset HM,
199 ten patients (47%) had at least one risk factor for developing HM including:
200 - Long term immunosuppressive treatments for renal ($n = 1$, tacrolimus) or liver transplantation
201 ($n = 6$), for a mean duration of 6 years before HM.

202 - HIV infection in 2 patients who developed Hodgkin Lymphoma, with a CD4 count of 168 and
203 1121/m³ respectively.

204 - Predisposing hematologic condition prior to DAA (cf. Table 1 Part B) (n=5)

205 Comparing patients with and without DAA, as described in the Table 1, Part A, proportion of
206 previous hemopathy at risk (benign or malignant) or past chemo or radiotherapy were not
207 different between groups. Concerning patients on chronic immunosuppressive treatments,
208 although proportions of transplanted patients were similar between groups, we found that liver
209 transplanted patients were more frequently found in the DAA group of patients. To note, no
210 congenital risk factor was described in both groups.

211 OUTCOME

212 As DAA were authorized only in 2012, follow up was shorter in the DAA+ group with a
213 median post HM-follow up time of 21.1 vs. 42.6 months (p = 0.024). At the cut-off date
214 (23/12/2020), in the DAA+ group, one patient did not require specific treatment, one was lost
215 to follow up, four achieved remission, six had stabilized their HM under treatment including 2
216 stem-cell transplantations (allogenic, n=1 and autologous, n=1) and nine died. Four of the five
217 AML cases in the DAA+ group died. Nonetheless, outcomes as blood marrow transplantation
218 requirement and mortality according to the Kaplan-Meier curves (Figure 2) did not

219 significantly differ between group DAA+ or - but it should be noted that the follow-up time
220 was shorter in the DAA+ group.

221 **DISCUSSION**

222 We described a total of 61 cases of HM in patients with a chronic HCV infection including 21
223 HM cases developing after the use of DAA. Our study highlights the following points for the
224 patients using DAA: (1) types of HM seemed to differ when comparing patients with or
225 without previous DAA, with a significant higher proportion of AML cases among patients
226 following DAA therapy.

227 (2) Of the 5 AML in the DAA+ group, three including two rare cases of Mixed-phenotype
228 Acute Leukaemia had no recognized risk factors.

229 (3) Three quarter of HM cases in the DAA treated patients occurred within two years after the
230 use of DAA.

231 To the best of our knowledge, no AML cases after DAA treatment have been reported yet. The
232 difference in frequency between the 2 groups of patients concerning the history of cirrhosis or
233 liver transplantation may represent a confusion bias, yet these characteristics have to date never
234 been associated with a higher risk of AML in the literature. Interestingly two of the five cases
235 of AML in the group DAA+ were of mixed-phenotype meaning that they present morphologic
236 and/or immunophenotypic characteristics of both myeloid and lymphoid lineages. These

237 MPAL usually represent only 4 to 8% of all acute Leukaemias and present an aggressive
238 clinical course, low complete remission and high recurrence rate (13). Both cases developed in
239 liver transplanted patients, although MPAL is not currently associated with solid organ
240 transplants nor immunosuppressive therapy. Therefore, our findings are quite astonishing and
241 need to be investigated by further studies. Furthermore, it may be of interest to know, that one
242 DAA + liver-transplanted case, with a NHL following DAA therapy treated by anthracyclines
243 developed secondarily an AML not registered in our study as developed after the cut-off date.
244 Previously described cases of HM following sustained viral response with DAA treatment
245 remain sparse but start to seek for awareness: To the best of our knowledge, no AML cases and
246 only six cases of either early occurrence or relapse of NHL have so far been described (14-18).
247 They occur in a time interval between 1 – 19 months after DAA treatment. None of these
248 patients had a liver transplantation.

249 Aside from liver transplantation, chronic hepatitis C infection is also known to be associated
250 with an increased risk of developing HM predominantly of B-cell type but not AML, whatever
251 the level of liver fibrosis (4, 11, 12, 19). The underlying pathogenesis is most likely the chronic
252 and continuous antigen stimulation leading to a permanent B-cell response with subsequent
253 genetic mutation and finally clonal and malignant B-cell proliferations (20). Another possible
254 explanation could be permanent B-cell damage induced either by HCV-derived viral protein

255 production inside B-cells or the transient intracellular infection (21). Viral eradication results in
256 hematological response in NHL in about two thirds of the cases suggesting a possible causal
257 connection between the HCV infection and the occurrence of lymphoma (22). Discordant
258 results were recently highlighted according to the influence of DAA on hematological risk
259 compared to the general population. A retrospective cohort study found a prevalence of NHL
260 after HCV DAA that was still 30-fold higher, (23). Another study points out that HCV viral
261 eradication with DAA may not be associated with a reduction in NHL risk in HCV population.
262 compared to the global population (24). Another one shows the disappearance of any higher
263 risk for all hematological cancer following DAA therapy (25). We also found B-cell type
264 lymphoma in cured HCV infections with DAA but at a weaker incidence than in patients
265 without DAA, which is consistent with a potential protective effect of viral eradication at an
266 early stage of the chronic infection, limiting the chronic inflammation and the risk of
267 developing lymphoma.

268 No formal hypothesis emerged yet for the cases of HM cases described. The persistence of
269 CD4 regulatory T cells, inhibiting CD8+ T-cells may be associated with a higher risk of
270 developing HM (26). Recently a study pointed a high level of vascular endothelium growth
271 factor (VEGF) after DAA treatment, which may accelerate tumor growth (27). Unfortunately,
272 no VEGF assay was performed in our cohort to corroborate this hypothesis.

273 Our study has several strengths. Hospital distribution of DAA allows capturing all patients
274 having received DAA since its authorization. We were able to analyse both hepatology and
275 haematology medical records for each patient, assure a long follow up duration and considered
276 multiple several confusion factors. We have been careful not to omit patients who have
277 benefited from treatment outside our hospital. But our study has limitations. First, information
278 collection was retrospective and therefore missing data or incorrect data may be an issue but no
279 variable exceeded 10% missing data. The number of included patients remains extremely small
280 which could result in a possible lack of power. No multivariate analysis was performed
281 because of the limited sample size and influence of a specific DAA could not be specifically
282 evaluated. According to univariate analysis, potential confounding factors may exist in our
283 study as patients in the DAA+ group had shorter follow-up time, more severe fibrosis/cirrhosis
284 and/or liver transplantation. However, all these factors are not known to be associated with
285 AML. Finally, we compared two groups of patients from different time sequences as DAA
286 treatment was progressively used in different schemes starting end of 2011. Therefore, our
287 results need to be taken with precaution and future larger studies are needed.

288

289

290 **CONCLUSION:**

291 In this comparative, retrospective and single-center study, we found, among HM in consecutive
292 HCV patients, an unexpected proportion of AML in patients treated with DAA treatment
293 compared to patients without DAA. AML cases included two rare mixed-phenotype forms.
294 Further studies including an ongoing multicentric observational study to confirm and explore
295 the results.

296 **ACKNOWLEDGEMENTS**

297 None

298 **FUNDING SOURCES**

299 No funding sources were perceived

300 **IMPLICATIONS**

301 CS and PL conceived the study.

302 EL, DAA and DRW helped with the acquisition of data

303 AD helped with the study design

304 All authors helped for the critical revision for important intellectual content and have approved
305 the final article.

306
307

308

309

310

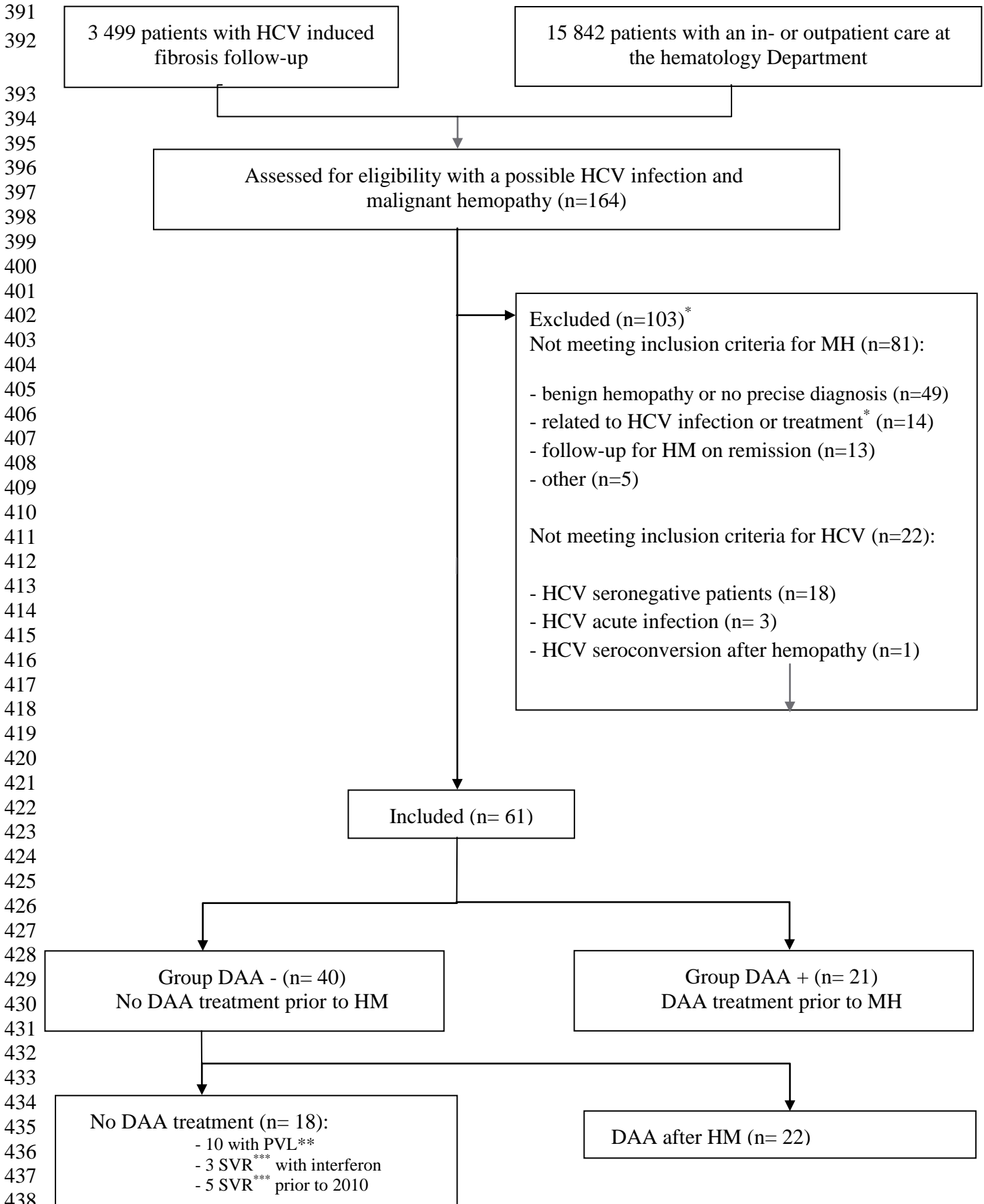
311
312
313
314
315
316
317
318
319
320
321
322
323
324
325
326
327
328
329
330
331
332
333
334
335
336
337
338
339
340
341
342
343
344
345
346
347
348
349
350
351
352
353
354
355
356
357
358
359
360
361
362
363
364
365
366
367
368

Bibliography

1. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. (2468-1253 (Electronic)).
2. Zaltron S, Spinetti A, Biasi L, Baiguera C, Castelli F. Chronic HCV infection: epidemiological and clinical relevance. *BMC Infect Dis.* 2012;12 Suppl 2:S2.
3. Hallager S, Brehm Christensen P, Ladelund S, Rye Clausen M, Lund Laursen A, Møller A, et al. Mortality Rates in Patients With Chronic Hepatitis C and Cirrhosis Compared With the General Population: A Danish Cohort Study. *J Infect Dis.* 2017;215(2):192-201.
4. Perz JF, Armstrong GL, Farrington LA, Hutin YJ, Bell BP. The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. *J Hepatol.* 2006;45(4):529-38.
5. World Health Organization. Guidelines for the Screening Care and Treatment of Persons with Chronic Hepatitis C Infection: Updated Version. 2016.
6. Spengler U. Direct antiviral agents (DAAs) - A new age in the treatment of hepatitis C virus infection. *Pharmacol Ther.* 2018;183:118-26.
7. Masarone M, Persico M. Hepatitis C virus infection and non-hepatocellular malignancies in the DAA era: A systematic review and meta-analysis. *Liver Int.* 2019.
8. Reig M, Mariño Z, Perelló C, Iñarrairaegui M, Ribeiro A, Lens S, et al. Unexpected high rate of early tumor recurrence in patients with HCV-related HCC undergoing interferon-free therapy. *J Hepatol.* 2016;65(4):719-26.
9. Kuo YH, Wang JH, Chang KC, Hung CH, Lu SN, Hu TH, et al. The influence of direct-acting antivirals in hepatitis C virus related hepatocellular carcinoma after curative treatment. *Invest New Drugs.* 2020;38(1):202-10.
10. Waziry R, Hajarizadeh B, Grebely J, Amin J, Law M, Danta M, et al. Hepatocellular carcinoma risk following direct-acting antiviral HCV therapy: A systematic review, meta-analyses, and meta-regression. *J Hepatol.* 2017;67(6):1204-12.
11. Giordano TP, Henderson L, Landgren O, Chiao EY, Kramer JR, El-Serag H, et al. Risk of non-Hodgkin lymphoma and lymphoproliferative precursor diseases in US veterans with hepatitis C virus. *JAMA.* 2007;297(18):2010-7.
12. Nieters A, Kallinowski B, Brennan P, Ott M, Maynadié M, Benavente Y, et al. Hepatitis C and risk of lymphoma: results of the European multicenter case-control study EPILYMPH. *Gastroenterology.* 2006;131(6):1879-86.
13. Naeim F. Chapter 13 - Acute Leukaemias of Ambiguous Lineage. In: Naeim F, Rao PN, Grody WW, editors. *Hematopathology.* Oxford: Academic Press; 2008. p. 279-86.
14. Samonakis DN, Psyllaki M, Pavlaki KI, Drakos E, Kehagias E, Tzardi M, et al. Aggressive recurrence of Non-Hodgkin's Lymphoma after successful clearance of hepatitis C virus with direct acting antivirals. *Ann Hepatol.* 2019.
15. Lin RJ, Moskovits T, Diefenbach CS, Hymes KB. Development of highly aggressive mantle cell lymphoma after sofosbuvir treatment of hepatitis C. *Blood Cancer J.* 2016;6:e402.
16. Andrade XA, Paz LH, Nassar M, Oramas DM, Fuentes HE, Kovarik P, et al. Primary Liver Diffuse Large B-Cell Lymphoma following Complete Response for Hepatitis C Infection after Direct Antiviral Therapy. *Acta Haematol.* 2018;139(2):77-80.
17. Rodríguez de Santiago E, Velázquez Kennedy K, García González M, Gea Rodríguez F, Téllez Villajos L, Tavío Hernández E, et al. HCV-positive lymphoma after sustained virological response with direct-acting antiviral agents: The game is not over after HCV eradication. *J Viral Hepat.* 2018;25(5):614-5.
18. Iwane K, Kayahara T, Takabatake H, Morimoto Y, Iseki A, Mizuno M, et al. [Recurrence of malignant lymphoma immediately after treatment for hepatitis C virus using direct-acting antivirals]. *Nihon Shokakibyō Gakkai Zasshi.* 2019;116(2):177-83.
19. Alkrekshi A, Kassem A, Park C, Tse W. Risk of Non-Hodgkin's Lymphoma in HCV Patients in the United States Between 2013 and 2020: A Population-Based Study. *Clin Lymphoma Myeloma Leuk.* 2021.
20. Marcucci F, Mele A. Hepatitis viruses and non-Hodgkin lymphoma: epidemiology, mechanisms of tumorigenesis, and therapeutic opportunities. *Blood.* 2011;117(6):1792-8.
21. Sakai H, Miwa T, Ikoma Y, Hanai T, Nakamura N, Imai K, et al. Development of diffuse large B-cell lymphoma after sofosbuvir-ledipasvir treatment for chronic hepatitis C: A case report and literature review. *Mol Clin Oncol.* 2020;13(3):1.

- 369 22. Arcaini L, Besson C, Frigeni M, Fontaine H, Goldaniga M, Casato M, et al. Interferon-free
370 antiviral treatment in B-cell lymphoproliferative disorders associated with hepatitis C virus infection.
371 Blood. 2016;128(21):2527-32.
- 372 23. Khoury J, Nassar G, Kramsky R, Saadi T. Extrahepatic Malignancies After Treatment with
373 Direct Antiviral Agents for Chronic HCV Infection. J Gastrointest Cancer. 2020;51(2):584-90.
- 374 24. El-Serag HB, Christie IC, Puenpatom A, Castillo D, Kanwal F, Kramer JR. The effects of
375 sustained virological response to direct-acting anti-viral therapy on the risk of extrahepatic
376 manifestations of hepatitis C infection. Aliment Pharmacol Ther. 2019;49(11):1442-7.
- 377 25. Lam JO, Hurley LB, Lai JB, Saxena V, Seo S, Chamberland S, Quesenberry CP, Champsi JH,
378 Ready J, Chiao EY, Marcus JM, Silverberg MJ. "Cancer in people with and without hepatitis C virus
379 infection: comparison of risk before and after introduction of direct-acting antivirals." Cancer Epidemiol
380 Biomarkers Prev. 2021; 30:2188-96.
- 381 26. Langhans B, Nischalke HD, Krämer B, Hausen A, Dold L, van Heteren P, Hüneburg R,
382 Nattermann J, Strassburg CP, Spengler U. Increased peripheral CD4+regulatory T cells persist after
383 successful direct-acting antiviral treatment of chronic hepatitis C. J Hepatol. 2017 May;66(5):888-896.
384 Albanian, English. doi: 10.1016/j.jhep.2016.12.019. Epub 2016 Dec 29. PMID: 28040549.
- 385 27. Villani R, Facciorusso A, Bellanti F, Tamborra R, Piscazzi A, Landriscina M, et al. DAAs
386 Rapidly Reduce Inflammation but Increase Serum VEGF Level: A Rationale for Tumor Risk during
387 Anti-HCV Treatment. PLoS One. 2016;11(12):e0167934.
- 388
- 389

390 **Figure 1: Flow Chart Diagram explaining the constitution of our groups**



439 * Detailed information can be found in the appendix, **PVL Persistent viral load, ***SVR, Sustained viral remission, HM= Hematological malignancy

441 **Table 1: Overall characteristics and per group**442 **Part A**

	Total (n=61)	Group DAA – (n = 40)	Group DAA+ (n = 21)	p-value
Age*	58.0 (17)	55.0 (14)	63.0 (17)	0.121
Female	18 (29.5%)	11 (27.5%)	7 (33.3%)	0.769
Co-infections				
HIV +	9 (14.8%)	7 (17.5%)	2 (9.5%)	0.473
HBV+	2 (3.3%)	2 (5.4%)	0 (0%)	1
Chronic hepatitis C				
All Genotypes				0.670
1	37 (60.7%)	21 (52.5%)	16 (76.5%)	
2	2 (3.3%)	1 (3%)	1 (4.8%)	
3	8 (13.1%)	6 (17%)	2 (9.5%)	
4	8 (13.1%)	6 (17%)	2 (9.5%)	
Unknown	6 (9.8%)	6 (15.0%)	0 (0%)	
Interferon treatment	34 (55.7%)	20 (50.0%)	14 (66.7%)	0.576
Time to HM diagnosis (y)**	8.3 (7.9)	5.8 (7.7)	12.1 (8.4)	0.020
Treatment duration (m)	12.0 (9.5)	9.50 (6.8)	14.0 (17.5)	0.100
Ribavirin treatment	38 (62.3%)	23 (57%)	15 (76.2%)	0.256
Time to HM diagnosis (y)**	8.0 (8.0)	6.3 (8.1)	9.9 (7.2)	0.100
Treatment duration (m)	9.00 (10.8)	7.50 (13.5)	11.5 (6.5)	0.677
Previous cirrhosis	23 (37.7%)	12 (30%)	11 (52.4%)	0.032
Risk factors for hematological malignancy				
Previous underlying hemopathy***	16 (26.2%)	9 (22.5%)	7 (33.3%)	0.376
Chemo- or radiotherapy	13 (21.0%)	9 (23%)	4 (19.0%)	1
Non-liver Transplantation	4 (6.5%)	3 (7.5%)	1 (6%)	1
Liver transplantation	13 (21.3%)	5 (12.5%)	8 (38.1%)	0.045
Time since transplant (y)	9 (5.0%)	10.8 (4.7)	6.0 (6.3)	0.604
For hepatocellular carcinoma	8 (13.1%)	4 (10.8%)	4 (19.0%)	0.576

443 Continuous variables are represented with their median and IQR in brackets. Binary variables are represented by their count and percentage in brackets.
444 Fisher's test or Wilcoxon – test used. DAA = Direct Acting Agents, HM= hematological malignancy. d= days, y= years, m=month. * Age at time of HM
445 diagnosis. **Defined as the time lapse between first specific treatment administration and diagnosis of HM, *** DAA+ group: Chronic lymphoid leukaemia
446 or hyperlymphocytosis (n=2), plasmablastic lymphoma (n=1), chronic myelomonocytic leukaemia (n=1), multiple myeloma (n=1), myelofibrosis (n=1),
447 AML in remission for at least 10 year with no recurrence during our study (n=1), DAA – group: Non Hodgkin Lymphoma (n=3), multiple myeloma (n=2),
448 AML (n=1, in remission for at least 10 years), myelofibrosis (n=1), myelodysplasia (n=2)
449

443
444
445
446
447
448
449
450
451
452
453

454
455

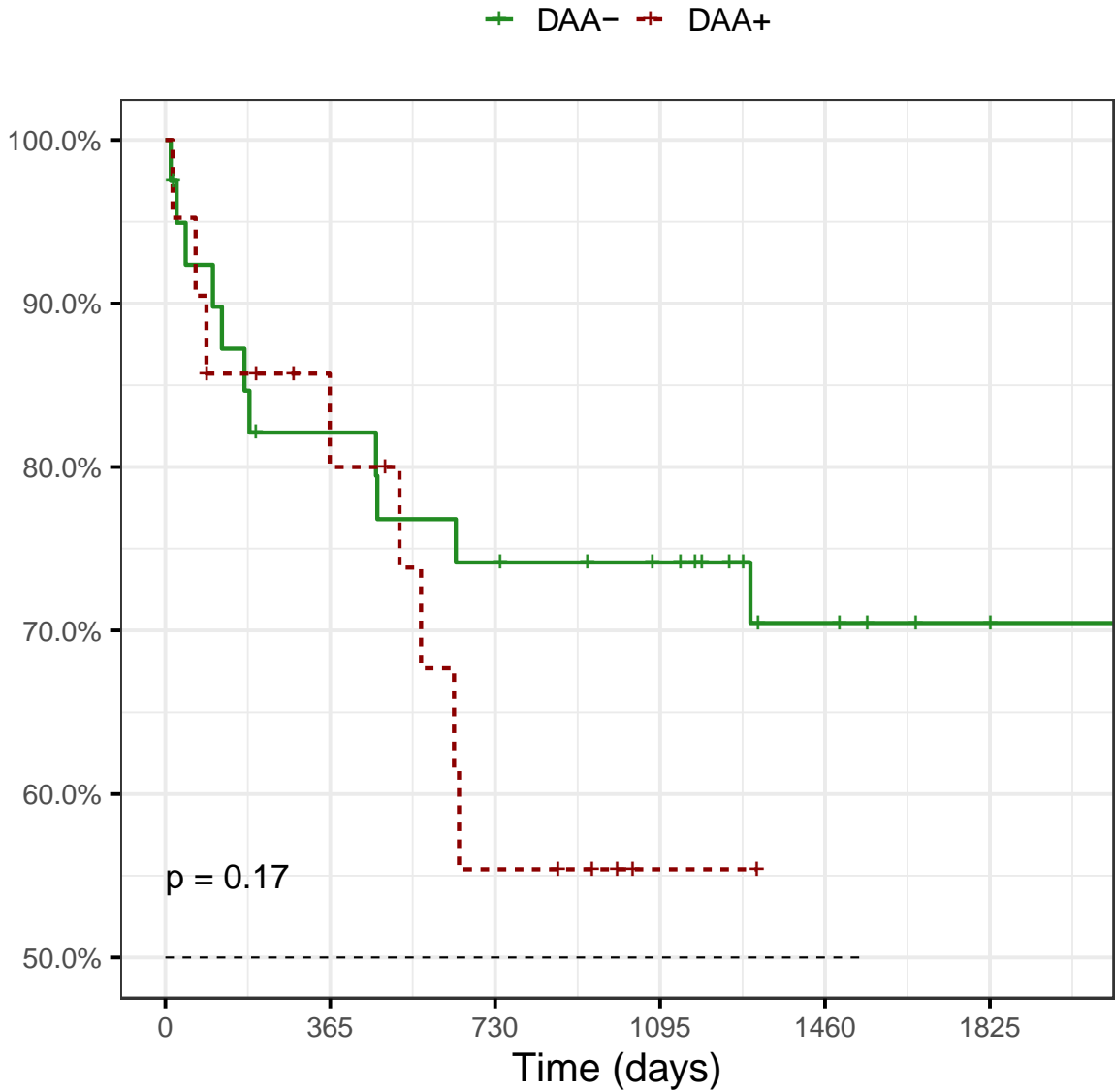
Part B

Hematological malignancy	Total (n=61)	Group DAA – (n = 40)	Group DAA+ (n = 21)	p-value
Lymphoid neoplasms				
Non-Hodgkin Lymphoma	28 (45.9%)	20 (50%)	8 (38.1 %)	0.427
Hodgkin’s Lymphoma	5 (8.2%)	3 (7.5%)	2 (9.5%)	0.629
Chronic lymphocytic Leukaemia	1 (1.6%)	0 (0%)	1 (4.8%)	0.298
Plasma-cell disorders				
Multiple Myeloma	7 (11.5%)	5 (12.5%)	2 (9.5%)	1
AL Amyloidosis	1 (1.6%)	0 (0%)	1 (4.8%)	0.298
Myeloproliferative neoplasm	9 (14.8%)	7 (17.5%)	2 (9.5%)	0.479
Myelodysplastic syndrome	2 (3.3%)	2 (5%)	0 (0%)	1
Acute Leukaemia				
Acute lymphoblastic Leukaemia	1 (1.6%)	1 (2.5%)	0 (0%)	1
Acute myeloid Leukaemia	7 (11.5%)	2 (5%)	5 (23.8%)	0.020
Including mixed phenotype	2 (3.3%)	0 (0%)	2 (9.5%)	
Grouping MH				
Lymphoid neoplasms [†]	35 (57.4%)	24 (60.0%)	11 (52.4%)	0.866
Plasma-cell disorders ^{††}	18 (29.5%)	11 (27.5%)	7 (33.3%)	
Myeloid neoplasm ^{†††}	8 (13.1%)	5 (12.5%)	3 (14.3%)	
Outcome				
Follow up since HM diagnosis (m)	36 (48.3)	42.6 (70.6)	21.1 (24.8)	0.024
Bone marrow transplantation	6 (9.8%)	3 (7.5%)	3 (14.3%)	0.822
Death	21 (34.4%)	12 (30.0%)	9 (42.9%)	0.17*

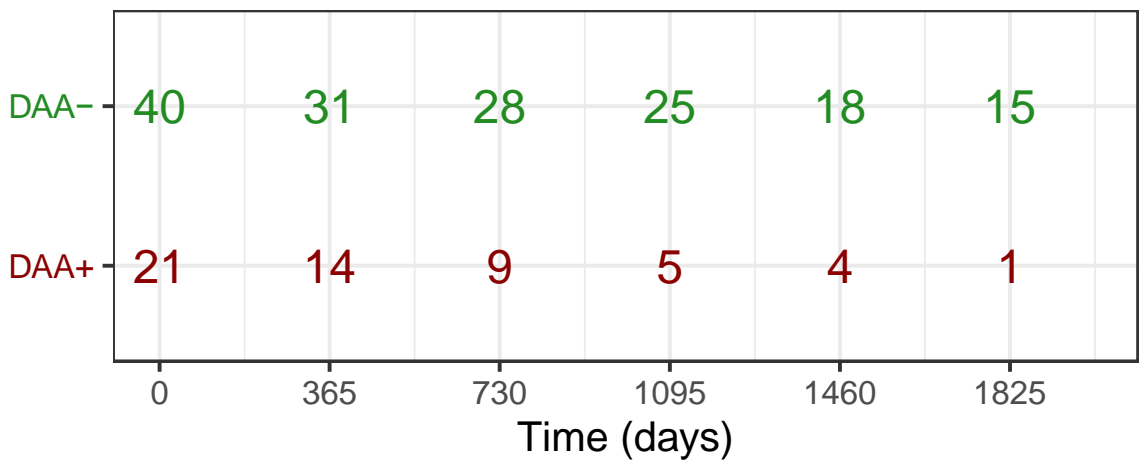
456
457
458
459
460
461
462
463
464
465

Continuous variables are represented with their median and IQR in brackets. Binary variables are represented by their count and percentage in brackets. Fisher’s test or Wilcoxon – test used. DAA = Direct Acting Agents, HM= hematological malignancy. d= days, y= years, m=month, * Cox test, † includes Non-hodgkin lymphoma, Hodgkin lymphoma, Chronic lymphocytic Leukaemia, ALL, †† includes Multiple myeloma, AL amyloidosis, ††† includes Myeloproliferative neoplasms, Myelodysplastic syndrome and AML

466 **Figure 2: Kaplan-Meier Survival curve after onset of MH between the group DAA + (red) and**



Number at risk



467 **DAA – (green) using the Cox model**

Table 2: Characteristics of AML

Group	Year	Sex	Age	Risk factors			Malignant hemopathy				HCV			Last DAA treatment			
				VIH	Previous MH	CtRt	Typ	GMT	FU	Metavir	Transplant	RBV	IFN	DAA lines	Type	Duration (d)	Delay to diagnosis*
DAA-	2014	M	65	No	CLL	Yes	AML	No	Death	F0	No	Yes	Yes		None		
DAA-	2016	M	60	Yes	RAEB II	No	AML	No	Death	F4	No	No	No		None		
DAA+	2016	M	58	No	No	No	AML	No	Death	F4	No	No	No	1	SofDac	90	M-19
DAA+	2015	M	63	No	Myelofibrosis	Yes	AML	No	Death	F0	No	Yes	Yes	2	SofDac	80	M-30
DAA+	2015	F	79	No	Myelofibrosis	Yes	AML	No	Death	F3	No	Yes	Yes	1	SofSim	89	M-14
DAA+	2017	M	51	No	No	No	AML + T	Yes	Remission	F4	Yes	Yes	Yes	3	SofDac	180	M-72
DAA+	2016	F	48	No	No	No	AML +B	Yes	Death.	F1	Yes	No	No	1	SofLed	176	M-23

HM= Hematological malignancy , 2nd=secondary character, GMT =graft marrow transplantation, CtRt=Previous chemo – or radiotherapy, BMT =Bone marrow transplant, FU= Outcome, LT= liver transplant, RBV= exposure to ribavirin, IFN= exposure to interferon, *Delay to diagnosis= time between the beginning of DAA treatment and MH diagnosis, SofDac= Sofosbuvir+Daclatasvir, SofSim=Sofosbuvir+Simeprevir, Tel=Telaprevir, Led=Ledipasvir, RAEB II= Refractory anemia with excess blasts type II, AML=Acute myeloid Leukaemia, MPAL= Mixed phenotypic acute Leukaemia

Table 3. Specific molecular characteristics of AML

Group	Precise Diagnosis	Caryotype	FLT3/NPM1	FISH	NGS mutations
DAA-	Therapy-related AML (t-AML)	47,XY,+1,der(1;7)(q10;p10),+8[13]/46,XY[7]	NA	del7q	NA
DAA-	AML-MRC	45,XY,-7[11]/46,XY[9]	NA	monosomy 7	NA
DAA+	AML with myelodysplasia-related changes (MRC)	46,XY,del(7)(q3?5)[8]/46,XY[12]	FLT3-/NPM1-	del7q	NA
DAA+	AML-MRC	48,XY,+12,+21[20]	FLT3-/NPM1-	tri12, tri21	ASXL1, GATA2, KRAS, PTPN11, SETBP1, SRSF2, STAG2
DAA+	AML, not otherwise specified (NOS)	46,XX[25]	NA	0	NA
DAA+	MPAL, T/myeloid, NOS	46,XY[20]	FLT3-ITD/NPM1-	0	0
DAA+	MPAL, B/myeloid, NOS	46,XX[20]	FLT3-ITD/NPM1-	0	FLT3-TKD, RUNX1

Supplemental data 1: Detail of Non-inclusion criteria

Benign hematological disorder or no accurate hematologic diagnosis (n=49)	Anemia of various etiologies (n=6): deficiency (n=2), unknown (n=2), inflammatory (n=1), multifactorial (n=1) Benign cytopenia (n=6): Moderate thrombocytopenia (n=2), lymphopenia (n=1), neutropenia (n=1), cytopenia linked to a viral infection (n=2) Hemolytic anemia with various etiologies (n=4): mechanic (n=1), autoimmune (n=1), unknown (n=2) MGUS (n=5) Porphyria (n=1) Drug related cytopenia (n=3) Benign ethnic neutropenia (n=3) Hemoglobinopathies: thalassemia (n=3), sickle-cell anemia (n=3), other (n=1) Hemochromatosis or hyperferritinemia (n=3) Benign adenopathy (n=4) Secondary polycythemia (n=5) Bleeding disorder (n=1) Multifactorial pancytopenia (n=1) Identical names (n=16) Negative HCV serology and viral load with birth dates in DAA list (n=2) Chart record error (n=1) Acute HCV infection (n=2) Seroconversion after hemopathy (n=1)
Absence of chronic HCV infection at time of MH diagnosis (n=22)	
Hemopathy related to HCV or HCV treatment (n=14)	HCV induced cytopenia (n=4) Thrombocytopenia due to hepatopathy (n=4) Pancytopenia due to Peginterféron alfa-2a (n=1) Interferon linked Hematologic toxicity (n=2) Ribavirin linked hemolytic anemia (n=1) Bone marrow failure linked to protease inhibitor (n=2)
Cured malignant MH (n=13)	Including bone marrow transplanted patients
Other (n=5)	Absence of patient (n=1) Preventive Follow up (bone marrow transplant were the donor developed later chronic lymphoid Leukaemia, n=1) Inpatient care for family history of multiple hematologic malignancies (n=1) HIV follow up (n=2)

Supplemental data 2: Last combined DAA effective therapy (n=21, group DAA +) The intersection size part represents the absolute number of combined therapy schemes and the lower part the absolute number per single molecule. Previous ligns when applicable are not represented.

