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25 **Summary**

26 Direct-acting antiviral use is associated with increased survival in hepatitis C-related
27 hepatocellular carcinoma patients. Patients treated with direct-acting antiviral who achieved
28 hepatitis C cure had additionally increased survival versus those treated with direct-acting
29 antiviral who did not achieve hepatitis C cure. This study supports the use of direct-acting
30 antiviral for hepatitis C treatment in hepatocellular carcinoma patients.

31

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36

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38 William Kamp - Data collection and analysis, writing of article, editing of article, final approval
39 of article

40 Cortlandt Sellers –Data collection and analysis, writing of article, editing of article, final approval
41 of article

42 Stacey Stein – Writing of article, editing of article, final approval of article

43 Joseph Lim – Writing of article, editing of article, final approval of article

44 Hyun Kim – Concept and design, supervision, funding, data analysis, writing of article, editing
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51

52 **Abbreviations**

53 DAA: Direct-acting antivirals; SVR12: 12-week sustained virologic response; HCC:

54 hepatocellular carcinoma; HCV: hepatitis c virus; OS: median overall survival; AJCC: American

55 Joint Committee on Cancer stage; MELD: Model for end stage liver disease; HR: hazard ratio

56 **Abstract:**

57 **Background:** To investigate the impact of direct-acting antivirals (DAA) and 12-week sustained
58 viral response (SVR12) in patients with hepatocellular carcinoma (HCC) and chronic hepatitis C
59 virus (HCV) infection. **Methods:** Retrospective analysis of HCC patients diagnosed from 2005
60 to 2016 at an urban tertiary-care hospital. Kaplan-Meier curves and multivariable Cox
61 proportional hazards models were used to assess survival. **Results:** 969 patients met inclusion
62 criteria. 478 patients received interventional oncology treatment (catheter-based therapies,
63 ablation or combination locoregional therapies), 141 received supportive care (palliative or no
64 treatment), 125 underwent liver transplantation, 112 had tumor resection and 94 received
65 chemotherapy or radiation as their primary treatment. Median overall survival of the cohort was
66 24.2 months (95% CI: 20.9-27.9). 470 patients had HCV (56%). 123 patients received DAA
67 therapies for HCV (26.2%), 83 of whom achieved SVR12 (68%). HCV-positive and HCV-
68 negative patients had similar survival (20.7 months vs 17.4 months, $p=0.22$). Patients receiving
69 DAA therapy had an overall survival of 71.8 months (CI: 39.5-not reached) vs 11.6 months (CI:
70 9.8-14.5) for patients without DAA therapy ($p<0.0001$). DAA patients who achieved SVR12 had
71 an overall survival of 75.6 months (CI: 49.2-not reached) vs the non-SVR12 group (26.7 months,
72 CI: 13.7-31.1, $p<0.0001$). Multivariable analysis revealed AJCC, Child-Pugh Score, MELD,
73 tumor size, tumor location and treatment type had independent influence on survival ($p<0.05$).
74 In HCV-positive patients, AJCC, MELD, tumor location, treatment allocation and DAA were
75 significant ($p<0.05$). In patients receiving DAA therapy, only MELD and SVR12 were predictive
76 of overall survival ($p<0.05$). **Conclusions:** DAA therapy and achieving SVR12 is associated
77 with increased overall survival in HCV patients with HCC.

78

79 **Introduction**

80 Hepatocellular carcinoma (HCC) represents a global public health burden, affecting an
81 estimated 14 million persons worldwide, and is the third leading cause of cancer mortality.¹
82 Within the United States, HCC is ranked 7th for cancer related mortality and has seen a doubling
83 in incidence from 1975 to 2007.^{1,2,3,4} The primary predisposing factors for HCC carcinogenesis is
84 liver cirrhosis.¹ Cirrhosis risk factors include chronic alcohol use, viral hepatitis, including
85 Hepatitis C (HCV), and non-alcoholic fatty liver disease.¹

86 Chronic HCV infection is the second most common risk factor for HCC and is
87 responsible for 10-25% of all HCC cases.¹ Over 20-30 years, 20-30% of patients with chronic
88 HCV infections will develop cirrhosis and end stage liver disease and 1-4% of these patients will
89 progress to HCC each year.^{5,6} Of all HCV related HCC cases, 80-90% occur in the setting of
90 cirrhosis.² With more than 3.5 million patients in the United States and an estimated 130-170
91 million patients worldwide currently infected with HCV, the importance of HCV management in
92 HCC therapeutic care and prevention is clear.^{7,8} The major current therapeutic goal for HCV and
93 prevention of liver disease progression is sustained viral response (SVR), which is defined by
94 negative HCV RNA at 12 weeks post-treatment (SVR12) and appears to be durable with a late
95 virologic relapse rate of less than 1%.^{9,10}

96 Therapeutic management of HCV has recently undergone a shifted from interferon-based
97 therapies to all-oral interferon-free direct-acting antiviral (DAA) combination regimens. DAAs
98 are a new class of drugs that target nonstructural proteins responsible for replication and
99 infection of the hepatitis c virus.^{10,11,12} Genotype specific DAA therapies have been shown to
100 reach SVR12 exceeding 90% of patients with fewer adverse effects compared with historic
101 interferon-based regimens.^{7,13,14,15,16,17,18} SVR12 from DAA regimens have been associated with

102 a decrease in liver outcomes including cirrhosis, hepatic decompensation, HCC and mortality.¹⁹
103 However, the impact of DAA regimens on clinical outcomes in patients with HCC remain
104 limited. This study evaluates the impact of DAA on overall survival in HCV patients with HCC
105 with the *a priori* hypothesis that SVR12 would be associated with improved outcome.

106

107 **Materials and Methods**

108 Study Cohort

109 Patient data were collected from those with prior consent to research participation and
110 institutional review board approval. Patients met criteria if they had a radiologic or
111 histopathologic HCC diagnosis defined by NCI/AASLD guidelines at Yale New Haven Hospital
112 between 2005 to 2016. Patients were grouped by primary HCC treatment including liver
113 transplantation, tumor resection, interventional oncological procedures (catheter-based therapies,
114 ablation or combination locoregional therapy), systemic management (chemotherapy or
115 radiation) and supportive care (palliative or no treatment). All patients were reviewed for history
116 of HCV infection diagnosis based on positive HCV antibody, positive HCV RNA and/or ICD-9
117 recorded in electronic medical records. Only those with a HCV infection diagnosis were assessed
118 for DAA treatment. Coinfections such as hepatitis B (HBV) and/or human immunodeficiency
119 virus (HIV) or prior HCV treatment with therapies other than DAA and/or use of multiple DAAs
120 did not preclude patients from analysis. SVR12 status was only collected for patients with HCV
121 plus any reported DAA use for HCV. Patients that reached SVR12 on interferon-based regimens
122 were not included with patients reaching SVR12 via DAA regimens. Exclusion criteria for this
123 study included unknown survival status and histopathologic diagnosis of combined HCC and
124 cholangiocarcinoma. Liver transplant patients were excluded from HCC, DAA and SVR12

125 overall survival and multivariable hazard ratio analyses. Patients were conservatively excluded in
126 analyses for which they had unknown values. The primary outcome of interest was overall
127 survival (OS), defined as time from HCC diagnosis to all-cause mortality or censoring.

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129 Statistical Analysis

130 Kaplan-Meier curves and Cox proportional hazards models were used to assess survival.
131 Univariate analysis of age, sex, Child-Pugh Score, tumor size, model for end-stage liver disease
132 (MELD), AJCC stage, body mass index, alpha-fetoprotein level, platelet count, unilobar or
133 bilobar tumor presentation, presence of multiple tumors, main treatment, HCV infection, DAA
134 treatment and SVR12 status were performed and variables with a p-value <0.2 were included
135 into multivariable analysis. Statistical analyses performed with JMP Pro 13.1.0 (SAS Institute,
136 Cary, North Carolina) and GraphPad Prism 8.0.0 (GraphPad Software, La Jolla, California).
137 Values were considered statistically significant with a p-value of less than 0.05.

138

139 Results

140 Cohort Description

141 Between 2005 and 2016, 969 HCC patients met inclusion criteria (Table 1). Mean age of
142 cohort at HCC diagnosis was 62.8±10.2 years. The group was predominately male at 79%. As
143 shown in Figure 1A, 478 patients (49.3%) received interventional oncology therapies, 141
144 (14.6%) received supportive care, 125 (12.9%) underwent liver transplantation, 112 (11.6%) had
145 tumor resection and 94 (9.7%) received chemotherapy and/or radiation as their primary
146 treatment. Among non-transplant patients, 470 (57.0%) patients were HCV positive of which
147 123 (26.2%) received a DAA regimen. Of those patients receiving DAAs for HCV treatment 83

148 (67.4%) achieved SVR12 (Figure 1B). Median OS for all patients was 24.2 months (95%
149 CI:20.9-27.9) (Figure 2A). Median OS for patients receiving liver transplantation (n=125) was
150 not reached as more than 50% of subgroup were alive at time of last follow up. Patients
151 undergoing tumor resection (n=112) had a median OS=56.7 months (95% CI: 41.9-103.5),
152 interventional oncology (IO) (n=478) median OS=27.7 (95% CI:22.3-30.7), systemic therapy
153 (n=94) median OS=5.6 months (95% CI: 4.4-7.3) and supportive management (n=141) median
154 OS=2.4 months (95% CI: 1.9-3.2, overall $p<0.0001$, figure 2B).

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156 **Fig. 1: A)** Treatment allocation of the entire hepatocellular carcinoma cohort **B)** Patients
157 stratified by HCV infection, DAA therapy, and achievement of SVR12

158 **Fig. 2: A)** Survival rate for all hepatocellular carcinoma (HCC) patients within cohort (n=969) in
159 months since HCC diagnosis. **B)** OS for HCC patients by main HCC treatment method. Patients
160 receiving liver transplantation (n=125). Patients undergoing tumor resection (n=112),
161 interventional oncology (IO) (n=478), systemic therapy (n=94) and supportive management
162 (n=141) (overall $p<0.0001$).

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171 **Table 1: Cohort and Subgroup Characteristics**

	Cohort	HCV Patients	Non-DAA Patients	DAA Patients	Non-SVR12 Patients	SVR12 Patients
Age at HCC Diagnosis (years) (mean±stdev)	62.8±10.2	60.5±7.7	59.9±7.7	61.7±5.8	61.6±5.3	61.8±6.1
Sex						
Male	768 (79.3%)	390 (83.0%)	202 (82.4%)	99 (80.5%)	28 (90.3%)	63 (75.9%)
Female	201 (20.7%)	80 (17.0%)	43 (17.6%)	24 (19.5%)	3 (9.7%)	20 (24.1%)
Liver Factors						
AJCC						
1	400 (43.8%)	198 (44.5%)	79 (34.5%)	79 (65.3%)	15 (48.4%)	58 (71.6%)
2	244 (26.7%)	110 (24.7%)	63 (27.5%)	31 (25.6%)	11 (35.5%)	19 (23.5%)
3	162 (17.7%)	86 (19.3%)	53 (23.1%)	8 (6.6%)	3 (9.7%)	4 (4.9%)
4	107 (11.7%)	51 (11.5%)	34 (14.8%)	3 (2.5%)	2 (6.5%)	0
Child Pugh Score						
A	512 (55.2%)	254 (56.3%)	116 (49.2%)	84 (68.9%)	24 (77.4%)	54 (65.9%)
B	284 (30.6%)	132 (29.3%)	80 (33.9%)	30 (24.6%)	6 (19.4%)	21 (25.6%)
C	132 (14.2%)	65 (14.4%)	40 (16.9%)	8 (6.6%)	1 (3.2%)	7 (8.5%)
MELD (mean±stdev)	11.4±5.7	10.7±4.6	11.4±5.2	9.5±3.4	9.3±3.1	9.67±3.5
Tumor Size (cm) (mean±stdev)	4.48±3.6	4.18±3.3	4.70±3.6	2.76±1.7	3.09±2.4	2.57±1.3
Tumor Location						
Unilobar	628 (66.7%)	298 (65.1%)	137 (57.6%)	93 (75.6%)	17 (54.8%)	68 (81.9%)
Bilobar	314 (33.3%)	160 (34.9%)	101 (42.4%)	30 (24.4%)	14 (45.2%)	15 (18.1%)
Multiple Tumors						
yes	442 (45.9%)	225 (48.4%)	133 (55.0%)	47 (38.2%)	19 (61.3%)	27 (32.5%)
no	520 (54.1%)	240 (51.6%)	109 (45.0%)	76 (61.8%)	12 (38.7%)	56 (67.5%)
Main Treatment						
Transplant	125 (13.2%)	0	0	0	0	0
Resection	112 (11.8%)	56 (12.1%)	21 (8.6%)	21 (17.4%)	5 (16.1%)	16 (19.5%)
IO	478 (50.3%)	285 (61.6%)	143 (58.4%)	93 (76.9%)	24 (77.4%)	63 (76.8%)
Systemic	94 (9.9%)	45 (9.7%)	26 (10.6%)	4 (3.3%)	1 (3.2%)	1 (1.2%)
Supportive	141 (14.8%)	77 (16.6%)	55 (22.4%)	3 (2.5%)	1 (3.2%)	2 (2.4%)
Hepatitis C Factors						
HCV Infection	551 (56.9%)	470	245	123	31	83
DAA Treatment		123 (26.2%)	0	123	31	83
SVR12				83 (67.5%)	0	83

172

173 **Table 1:** Characteristics of cohort, HCV, non-DAA, DAA, non-SVR12 and SVR12 subgroups, n

174 (%) or mean ± standard deviation as marked. AJCC: American Joint Committee on Cancer stage,

175 MELD: model for end stage liver disease, IO: interventional oncology, HCV: hepatitis C, DAA:
176 direct-acting antivirals, SVR12: sustained viral response at 12 weeks.

177

178 Overall Survival in HCV and DAA Subgroups

179 Subgroup analysis of HCV patients, recipients of DAA and those that achieved SVR12
180 revealed significant influences on OS. Although patients with and without HCV showed no
181 significant difference in survival: median OS 20.7 months (95% CI: 16.5-24.1) versus 17.4
182 months (95% CI: 13.0-20.6) respectively, (p=0.22), HCV patients that received DAA had a
183 median OS of 71.8 months (95% CI: 39.5-not reached) compared to 11.6 months (95% CI: 9.8-
184 14.5) for HCV patients that did not use DAAs (p<0.0001)(Figure 3). Patients achieving SVR12
185 had a higher median OS of 75.6 months (95% CI: 49.2-not reached) versus 26.7 months (95%
186 CI: 13.7-31.1) for patients with positive HCV RNA by PCR 12 weeks post-DAA cessation
187 (Figure 3C) (p<0.0001).

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189 **Fig. 3: Patient survival rate in months since hepatocellular carcinoma (HCC) diagnosis. A)**

190 HCC Patients with positive history of hepatitis c (HCV) infection (n=470) versus patients with
191 no history of HCV (n=363) (p=0.22) **B)** HCC and HCV patients that received a direct-acting
192 antiviral (DAA) (n=123) versus those who did not receive a DAA (n=247) (p<0.0001) **C)**
193 Patients with HCC and HCV that received a DAA and achieved sustained viral response
194 (SVR12) (n=83) versus those who did not achieve SVR12 (n=31) (p<0.0001).

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196 Prognostic Factors

197 Multivariable analyses of subgroups were performed to assess impact of relevant HCC
198 prognostic markers, HCC therapies, HCV factors and lab values. Within all non-transplant
199 patients, numerous factors significantly influenced overall survival (Figure 4A, Table 2). AJCC
200 stage 4 had decreased survival compared to stage 1 (HR=2.77, 95% CI:1.86-4.08, p<0.0001) and
201 2 (HR=2.06, 95% CI: 1.40-3.01, p=0.0003). AJCC stage 3 also had poorer survival as compared
202 to stage 1 (HR=2.29, 95% CI: 1.26-2.30, p<0.0001) and 2 (HR=1.70, 95% CI: 1.26-2.30,
203 p=0.0005). AJCC stage 2 had a HR=1.34 (95% CI: 1.03-1.75, p=0.03) compared to stage 1.
204 Increased Child-Pugh score was also associated with worsened survival (Child Pugh C vs. A: HR
205 1.69, 95% CI: 1.07-2.65, p=0.02; B vs A: HR 1.83, 95% CI: 1.43-2.233, p<0.0001), as were
206 increased MELD score, increased tumor size, and bilobar tumors (p<0.05). Treatment allocation
207 significantly impacted survival, with resection demonstrating improved survival vs interventional
208 oncology (HR=0.56, 95% CI: 0.39-0.81, p=0.002), systemic therapies (HR=0.26, 95% CI:0.16-
209 0.42, p<0.0001) and supportive management (HR=0.12, 95% CI:0.08-0.19, p<0.0001).
210 Interventional oncology increased survival rates over systemic therapies (HR=0.46, 95%
211 CI:0.33-0.65, p<0.0001) and supportive management (HR=0.22, 95% CI:0.16-0.29, p<0.0001).
212 Systemic therapies showed improved survival rates over supportive therapies (HR=0.47, 95%
213 CI:0.42-0.68, p<0.0001).

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220 **Table 2: Hazard Ratios for Cohort and HCV and DAA subgroups**

	Total	HCV	DAA
Sex - Male/Female	1.25 (0.99-1.49, p=0.0592)	1.28 (0.89-1.89, p=0.1924)	1.30 (0.39-5.25, p=0.6799)
Liver Factors			
MELD	1.03 (1.00-1.06, p=0.0168)	1.05 (1.00-1.11, p=0.0468)	1.21 (1.02-1.44, p=0.0326)
Tumor Size	1.06 (1.02-1.09, p<0.0007)	1.01 (0.95-1.06, p=0.08082)	0.75 (0.49-1.06, p=0.1044)
Bilobar/Unilobar	1.32 (1.03-1.69, p=0.026)	1.62 (1.14-2.30, p=0.0072)	1.38 (0.36-5.51, p=0.6354)
Multiple Tumors - yes/no	1.03 (0.80-1.32, p=0.816)	1.27 (0.88-1.83, p=0.1986)	1.01 (0.41-2.99, p=0.9831)
AJCC			
4/1	2.77 (1.86-4.08, p<0.0001)	1.59 (0.79-3.09, p=0.19)	
4/2	2.06 (1.40-3.01, p=0.0003)	1.32 (0.67-2.53, p=0.4209)	
4/3	1.21 (0.86-1.68, p=0.2704)	0.75 (0.42-1.31, p=0.3186)	
3/1	2.29 (1.69-3.09, p<0.0001)	2.11 (1.25-5.54, p<0.0051)	1.81 (0.08-13.48, p=0.6350)
3/2	1.70 (1.26-2.30, p=0.0005)	1.76 (1.05-2.92, p=0.0328)	2.28 (0.10-19.85, p=0.5336)
2/1	1.34 (1.03-1.75, p=0.0305)	1.20 (0.79-1.82, p=0.3872)	0.80 (0.27-2.22, p=0.6658)
Child-Pugh Score			
C/A	1.69 (1.07-2.65, p=0.0235)	0.86 (0.42-1.73, p=0.6775)	0.13 (0.01-1.55, p=0.1068)
C/B	0.93 (0.63-1.35, p=0.6904)	0.65 (0.36-1.18, p=0.1549)	0.15 (0.01-1.67, p=0.1234)
B/A	1.83 (1.43-2.33, p<0.0001)	1.33 (0.92-1.91, p=0.1351)	0.85 (0.30-2.40, p=0.7584)
Main Treatment			
Resection/IO	0.56 (0.39-0.81, p=0.0019)	0.79 (0.42-1.36, p=0.4118)	0.39 (0.05-1.92, p=0.2649)
Resection/Systemic	0.26 (0.16-0.42, p<0.0001)	0.29 (0.13-0.64, p=0.002)	
Resection/Supportive	0.12 (0.08-0.19, p<0.0001)	0.12 (0.06-0.25, p<0.0001)	0.12 (0.00-5.53, p=0.2586)
IO/Systemic	0.46 (0.33-0.65, p<0.0001)	0.37 (0.21-0.68, p=0.0017)	
IO/Supportive	0.22 (0.16-0.29, p<0.0001)	0.16 (0.10-0.26, p<0.0001)	0.31 (0.01-9.82, p=0.4652)
Systemic/Supportive	0.47 (0.32-0.68, p<0.0001)	2.34 (1.23-4.52, p=0.0093)	
Hepatits C Factors			
HCV Infection - yes/no	0.85 (0.70-1.04, p=0.1151)		
DAA Therapy - yes/no		0.39 (0.26-0.58, p<0.0001)	
SVR12 Attained - yes/no			0.14 (0.06-0.35, p<0.0001)

221

222 **Table 2:** Hazard ratios from multivariable analysis. HR, 95% Confidence Interval, p-value,

223 AJCC: American Joint Committee on Cancer stage, MELD: model for end stage liver disease,

224 IO: interventional oncology, HCV: hepatitis C, DAA: direct-acting antivirals, SVR12: sustained

225 viral response at 12 weeks.

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227

228 Multivariable analysis of non-transplant HCV patients showed similar results to non-
229 transplant patients (Figure 4B) with the addition of DAA use as a significant prognostic marker
230 (HR=0.39, 95% CI:0.26-0.58, $p<0.0001$). In the final subgroup, including only DAA patients,
231 only two factors were significant, MELD (HR=1.21, 95% CI:1.02-1.44, $p=0.03$) and SVR12
232 (HR=0.14, 95% CI:0.06-0.35, $p<0.0001$).

233

234 **Fig. 4: Hazard ratios from multivariable analysis on overall survival in non-transplant**

235 **HCC patients.** Values greater than one indicate increased risk of death. Values less than one

236 indicate reduced risk of death. **A)** Hazard ratios in all non-transplant HCC patients. **B)** Hazard

237 ratios in all non-transplant HCC with history of HCV. * $=p<0.05$, AJCC: American Joint

238 Committee on Cancer stage, MELD: model for end stage liver disease, AFP: alpha-fetoprotein,

239 IO: interventional oncology, HCV: hepatitis C, DAA: direct-acting antivirals.

240

241 **Discussion**

242 With the increasing incidence and prevalence of HCC and the impact of HCV infection on
243 development of cirrhosis and HCC tumor formation, the importance of understanding the effects
244 of DAA in HCC patients is only becoming more vital. One-half of the HCC cases among the
245 three-fold increase in HCC incidence between 1975 and 2007 in the US can be attributed to the
246 aging chronic HCV population.² Although there are indications that DAAs may slow progression
247 to HCC,^{20,21} there remains a vast population of HCC patients that could potentially benefit from
248 treatment of their chronic HCV infections.

249 It is likely that the improved median overall survival seen in our cohort among HCC

250 patients taking DAAs is a direct result of the high success rate of achieving SVR12. Although

251 more patients are needed to reduce the possible influence of DAA exclusion from patients with
252 worse prognoses, the over three-fold difference in median overall survival between those that did
253 and did not achieve SVR12 likely indicates profound longitudinal effects of HCV cure in HCC
254 patients. Although our data indicates less severe HCC and liver disease in DAA and SVR12
255 patients versus their subgroup counterparts, multivariable
256 analysis supports reduced all-cause mortality in patients receiving DAAs and achieving SVR12.
257 In addition, others have reported that achieving SVR12 is associated with improved liver
258 function, Child-Pugh scores and reversal of liver decompensation symptoms which could also be
259 factors in the improved survival.^{22,23}

260 Reaching SVR12 is not an easy task in the HCC patient population. Only 69% of our
261 population reached SVR12 with similar results in other retrospective analyses of DAA use in
262 HCC patients^{24,25} compared to reported values of over 90% in populations powered to DAA
263 efficacy.¹⁸ Part of this may be due to the difficulty of integrating HCV treatment into HCC care,
264 as demonstrated by the low rate of HCC patients with HCV receiving DAA treatment in our
265 cohort (<50%). While there is currently much discussion as to how aggressive clinicians should
266 be about treating active HCV in HCC patients, no official guidelines currently exist.^{23,26}
267 Frequently, HCC management supersedes HCV treatment as many providers seek to triage HCV
268 until after the cancer has been treated.²³ In addition, debate is ongoing as to whether or not DAA
269 use increases HCC recurrence rates.^{18,20,27,28,29, 30}

270 Interestingly, our results suggest that there is ample time for HCV intervention in newly
271 diagnosed HCC patients. The DAA treatment course typically 8-24 weeks,³¹ and patients
272 receiving resection or IO treatments, 74% of our cohort population, had a median overall
273 survival greater than 27 months. We are hopeful that conversion from non-DAA to DAA

274 medications and subsequent SVR12 achievement will increase as awareness and use of DAA in
275 current HCV management increases.

276 This cohort also raises important questions for future research. The patients achieving SVR12
277 with DAA include those that had previously failed interferon-based therapies and subsequently
278 received DAA after their introduction, those that received multiple courses and combinations of
279 DAA and those that received DAA for different lengths of time. Some received DAA during
280 HCC management while others received DAA before their HCC diagnosis. More work is needed
281 in areas concerning the differences in DAA regimen efficacy to understand the most appropriate
282 combination of DAA and regimen length and then tailor these by HCV genotype, HCC
283 prognosis and other host and genetic factors in order to help more patients achieve SVR12 and
284 better overall outcomes.

285

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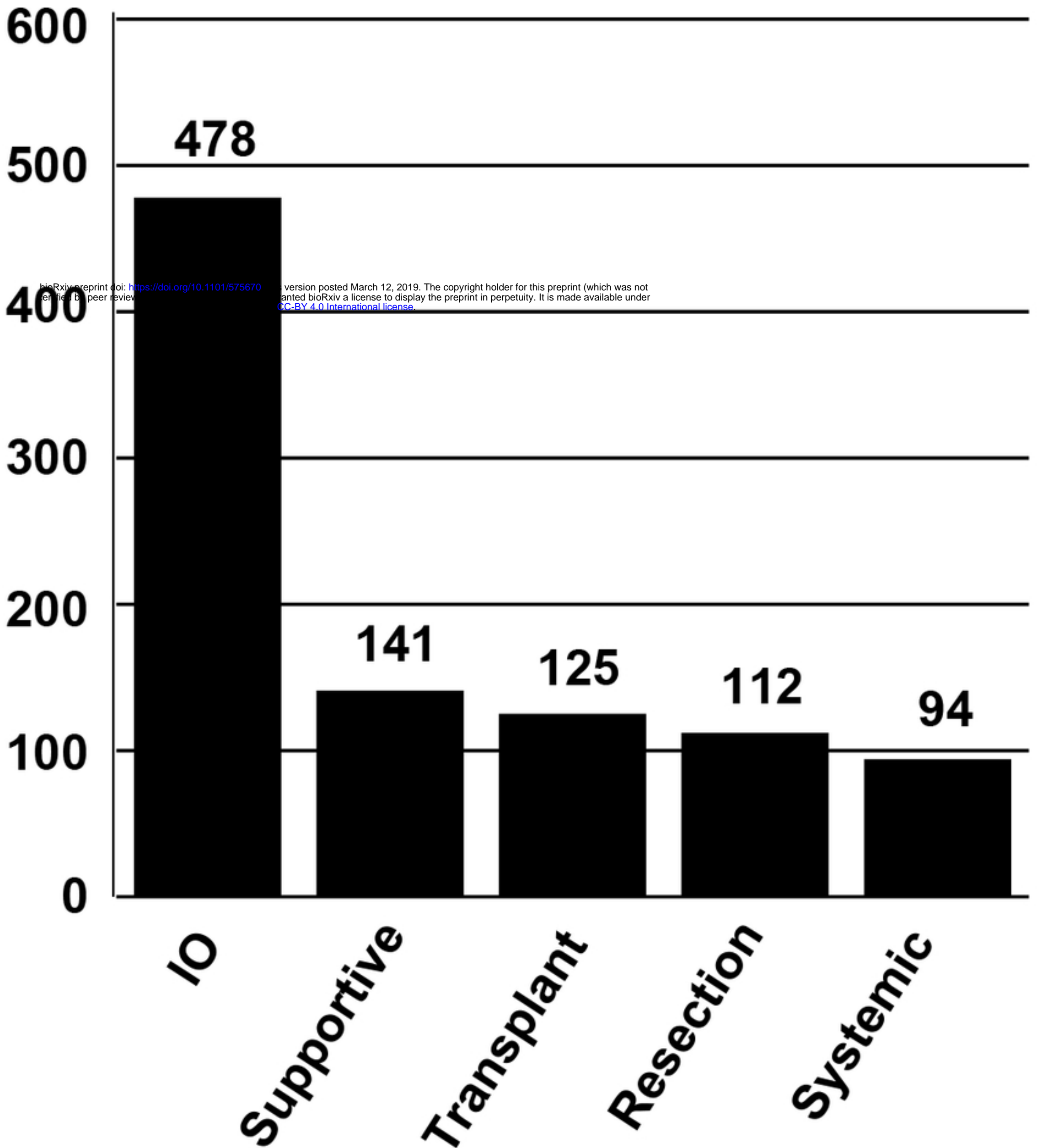
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Figure 1a

900

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825

800

700

600

500

400

300

200

100

0

470

123

83

Total

HCV

DAA

SVR12

Figure 1b

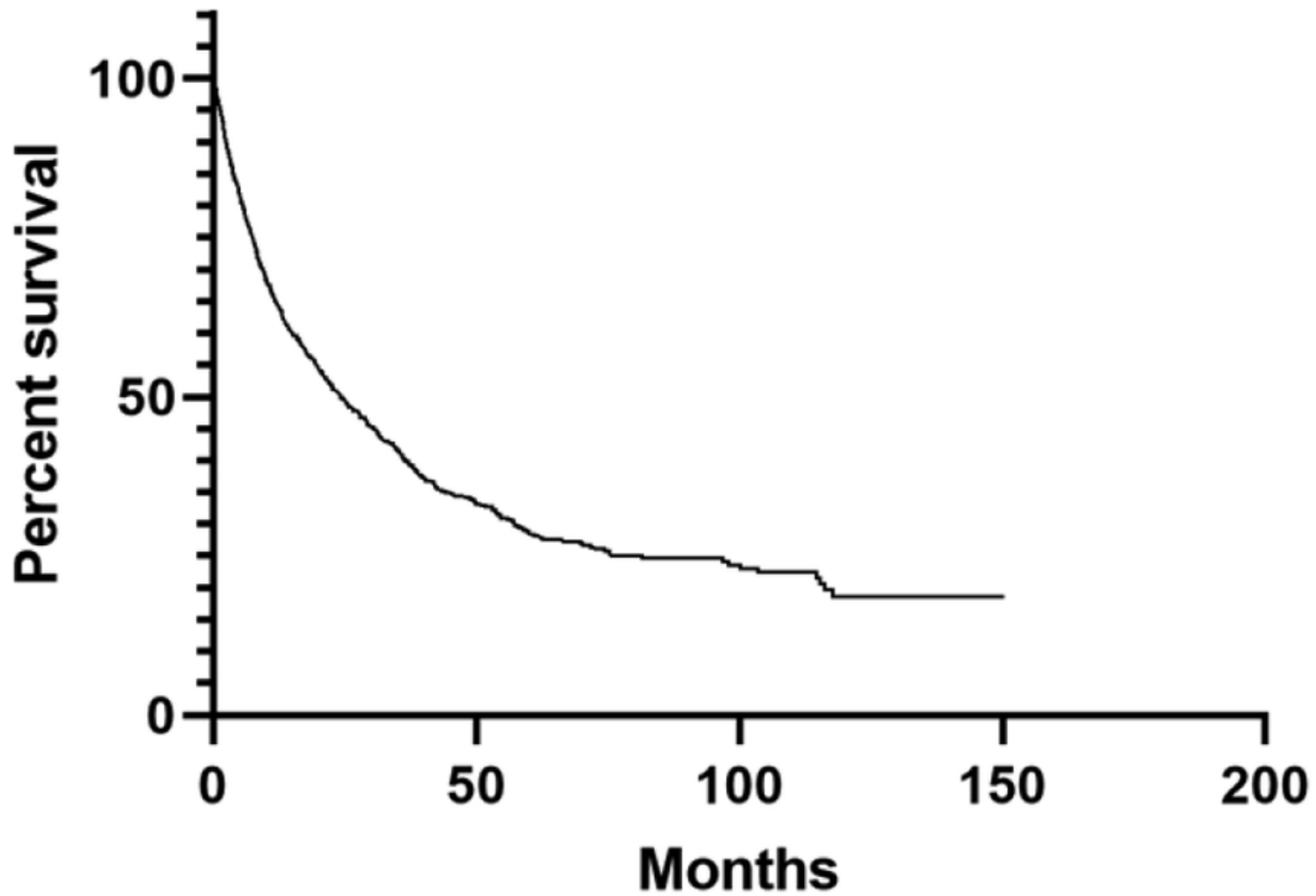


Figure 2a

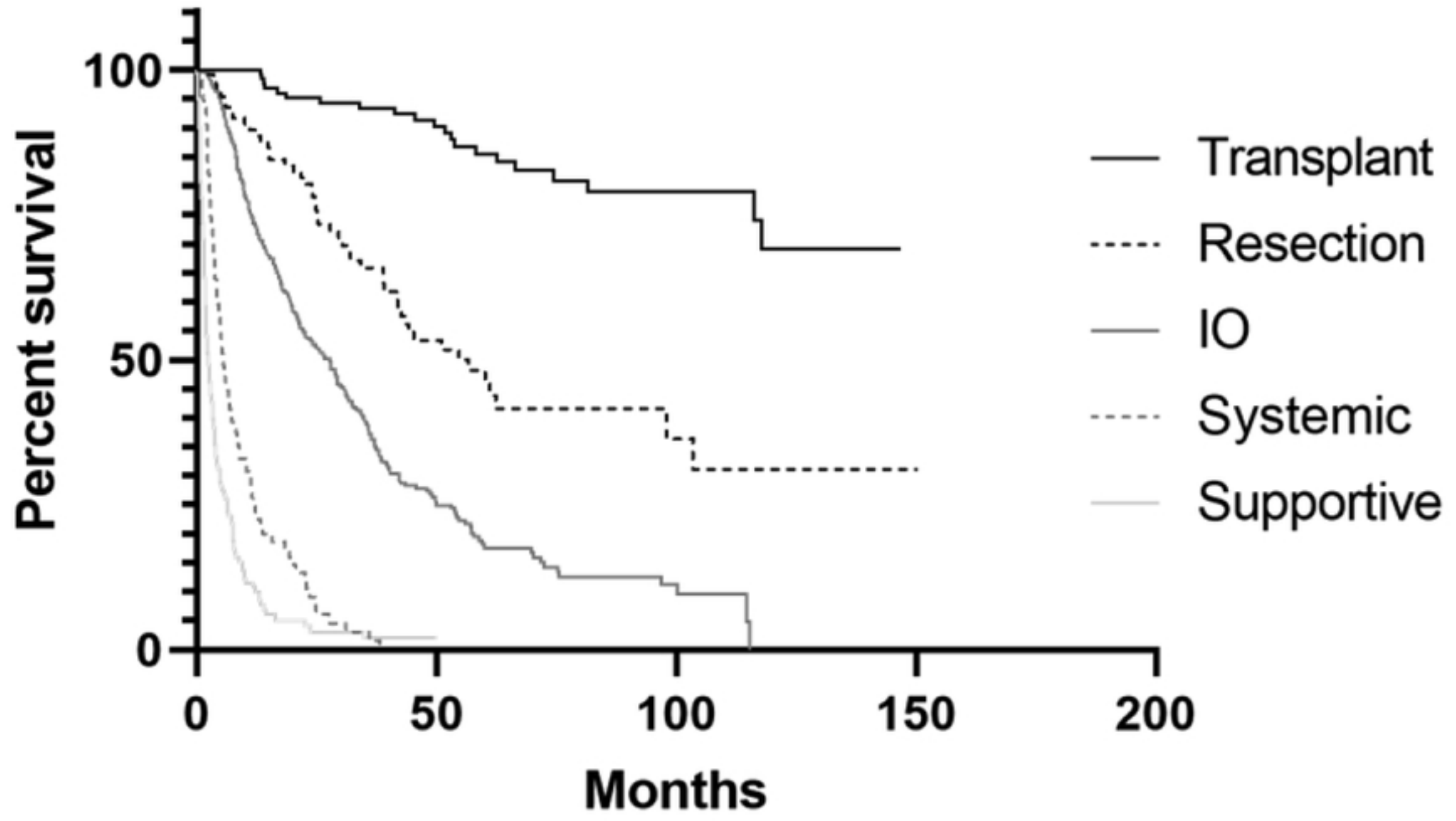


Figure 2b

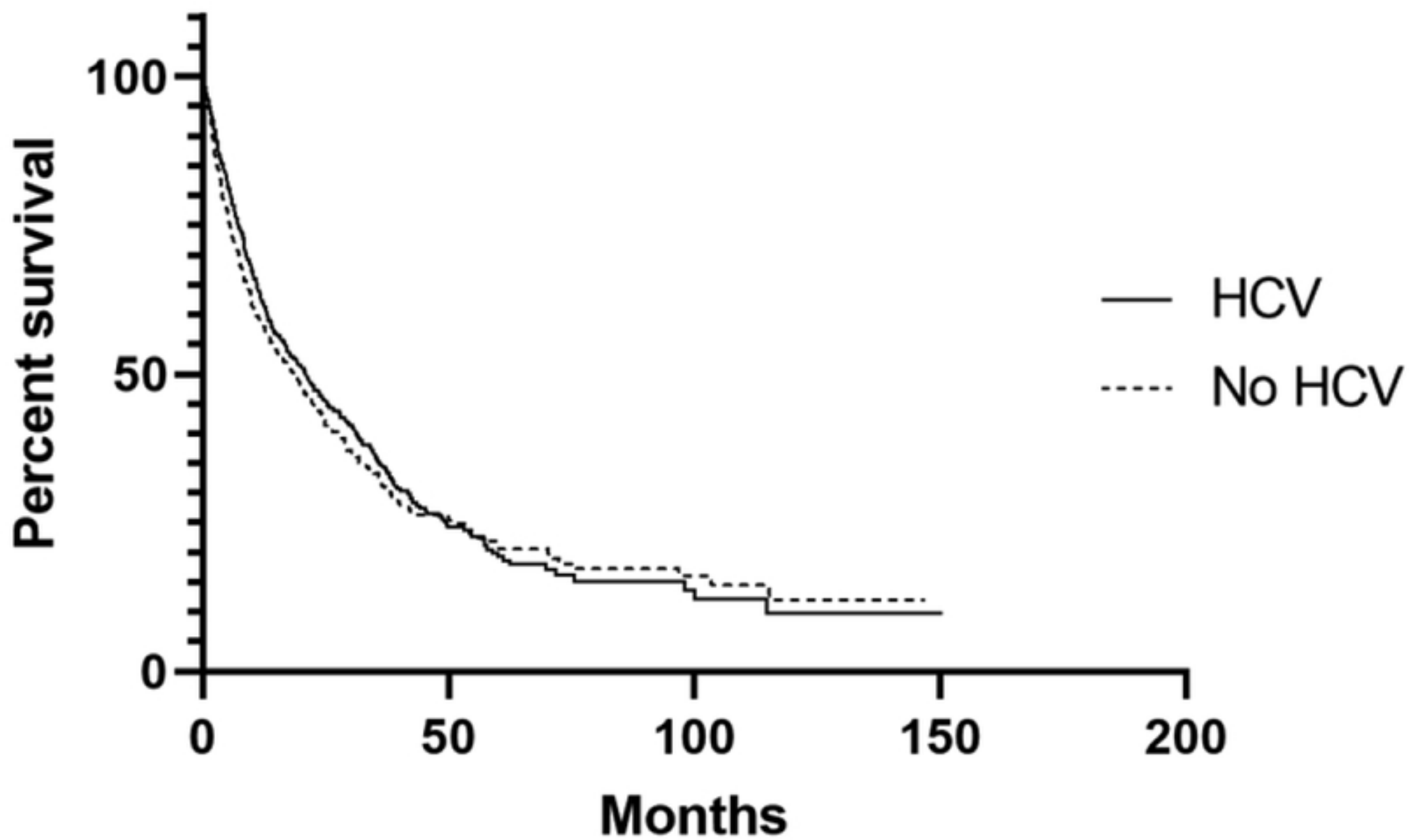


Figure 3a

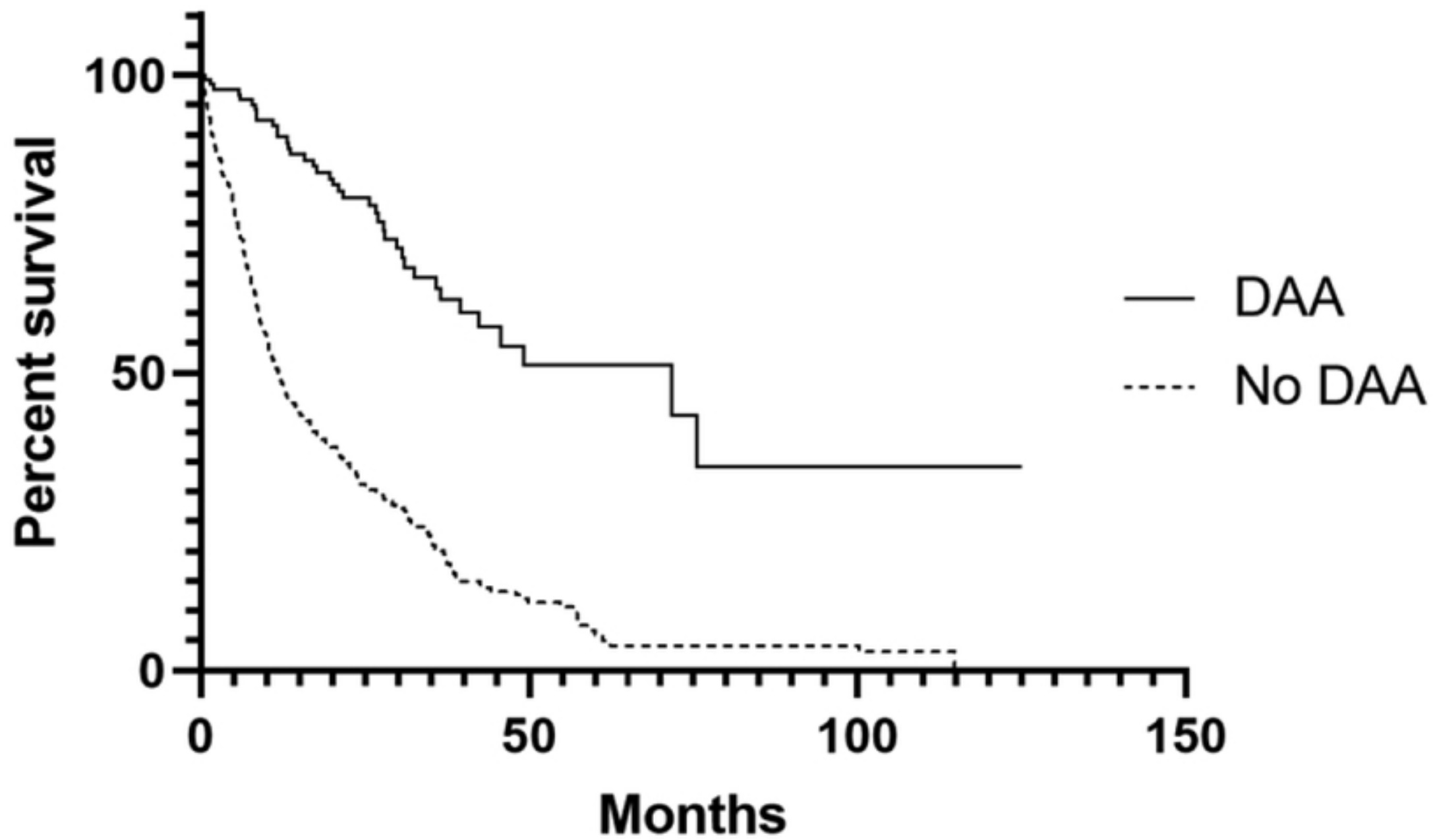


Figure 3b

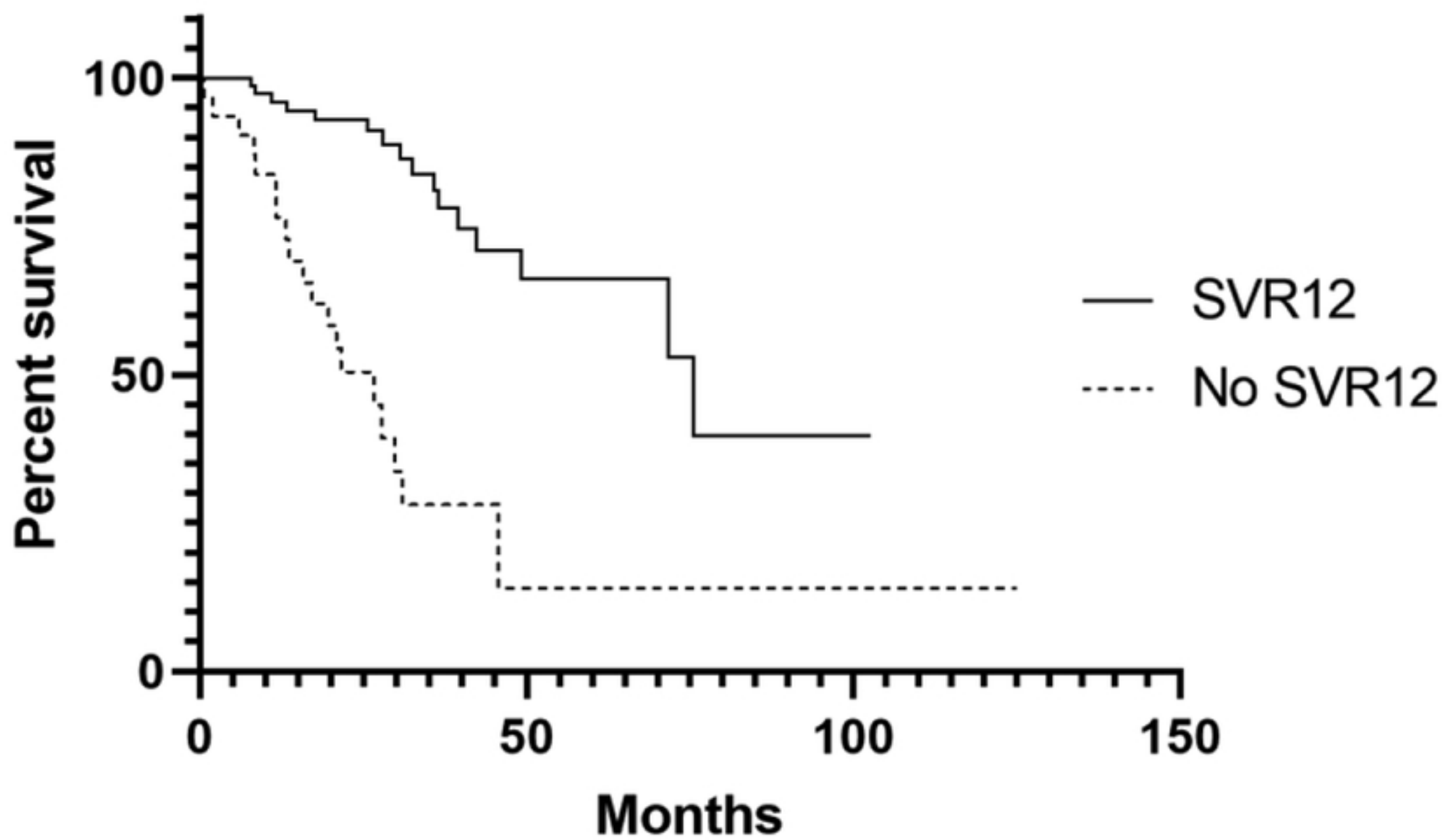


Figure 3c

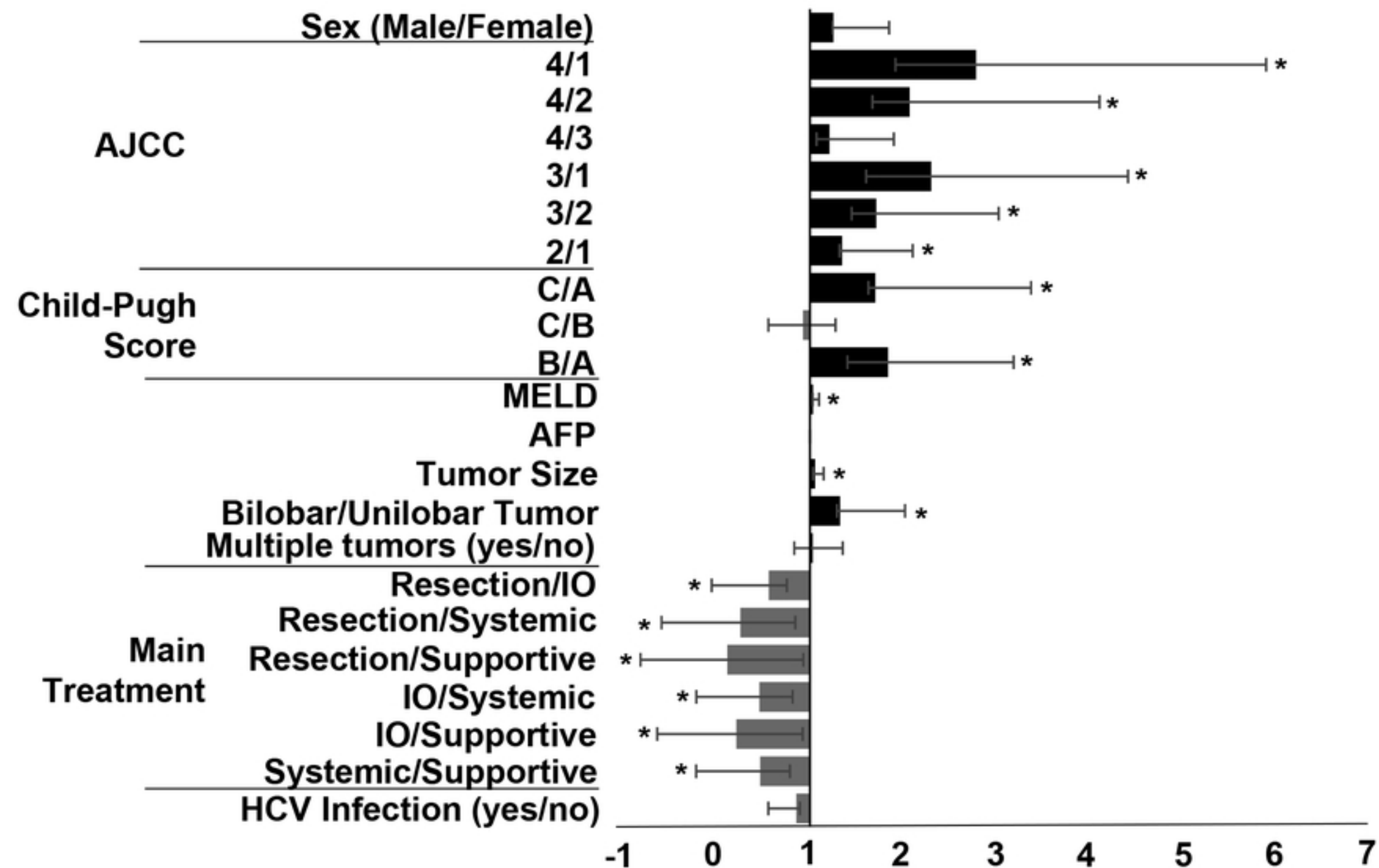


Figure 4a

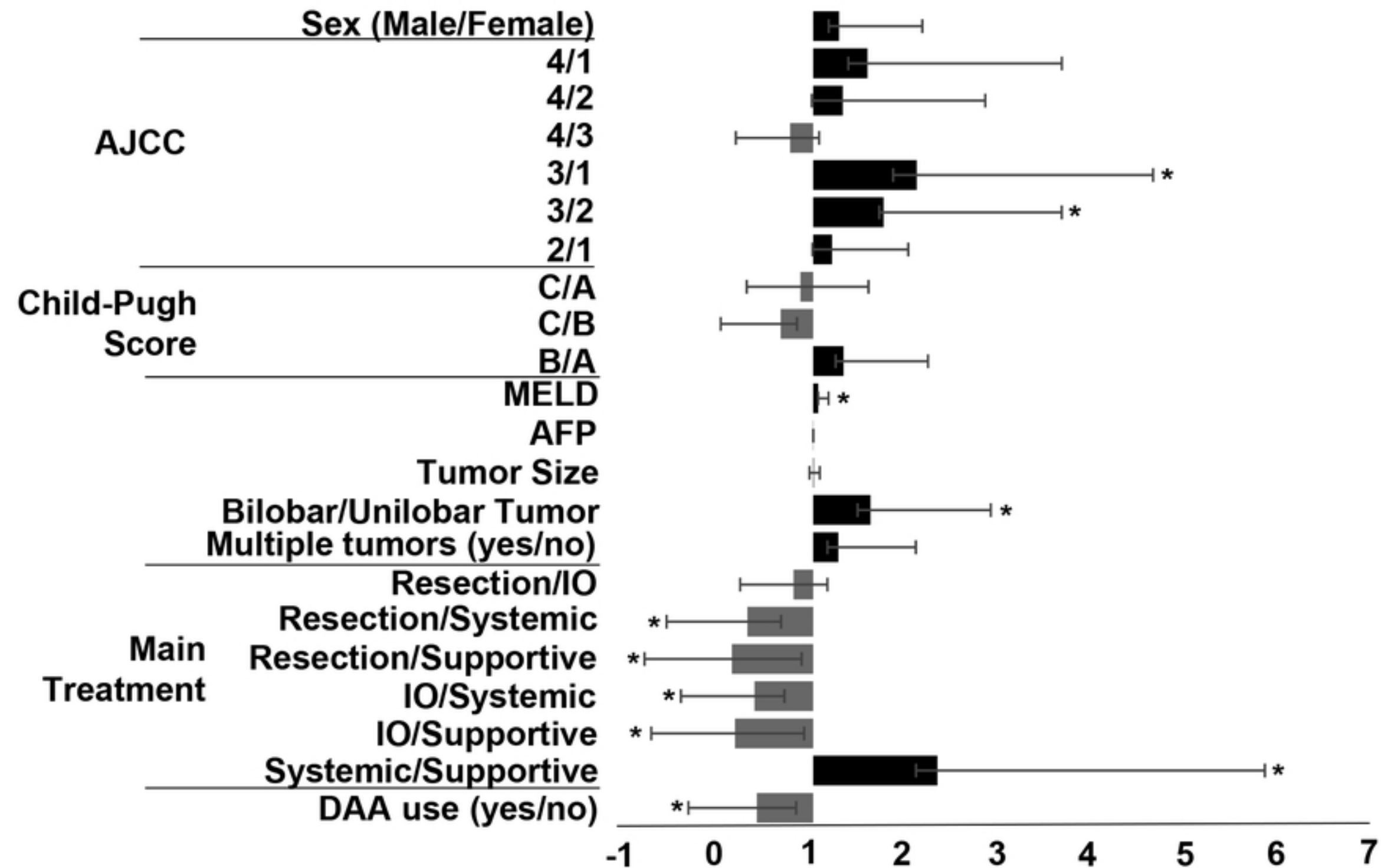


Figure 4b