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Hepatitis Associated Aplastic Anaemia: Epidemiology and Treatment Results obtained in Europe. A Report of The EBMT Aplastic Anemia Working Party

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Running title : **Epidemiology and treatment results in Hepatitis-Associated Aplastic Anemia**

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Key words : **Hepatitis-associated Aplastic Anemia, Immunosuppression, Bone Marrow Transplantation**

ABSTRACT

Aim: assess the epidemiology of Hepatitis-Associated Aplasia (HAA) and compare treatment outcome of HAA with non-HAA patients.

Patients. We evaluated 3916 aplastic anemia patients reported to the European Registry between 1990 and 2007. Year, month, season of diagnosis, type and outcome of first line therapy were analyzed.

Results. Prevalence of HAA (n=214) in Europe was 5%. HAA patients, compared to non-HAA were younger (15 vs 20 years, $p<0.001$), with a male prevalence (68% vs 58% $p=0.002$), and were treated earlier after diagnosis (46 vs 62 days; $p<0.001$). No significant differences were found according to the year or month of diagnosis. No geographic clusters could be identified. Actuarial survival at 10 years after first line immunosuppression was 69%, and did not differ according to etiology. The 10 year actuarial survival after transplantation was 70%, and was comparable in HAA and non-HAA patients, when stratified for age and donor type. In a multivariate COX analysis, increasing age and delayed treatment were significant negative indicators for survival.

Conclusions. The incidence of HAA is 5% and is evenly distributed over time and geographic areas in Europe. Treatment outcome, and predictive variables, are comparable in patients with or without HAA.

INTRODUCTION

Acquired aplastic anemia is a rare and severe disease, which may be fatal, if left untreated. Most cases of acquired severe aplastic anaemia (SAA) are not associated with any known cause, and are therefore classified as idiopathic. A small proportion of patients, however, will develop pancytopenia following an acute episode of hepatitis, and this is referred to as hepatitis-associated aplastic anaemia (HAA; Brown KE *et al*, 1997). Indeed, clinically apparent hepatitis precedes Aplasia by a period of weeks to months, typically in young males. Although hepatitis usually, but not always, follows a benign and unremarkable course, the subsequent aplasia, if not treated, is often fatal. As to the frequency of HAA, it varies according to the geographic area: a prior episode of hepatitis is reported in 2-5% of aplastic patients in Europe and North America series, while its occurrence is up to 10% in Far East Countries (Baumelou E *et al*, 1993; Young NS *et al*, 1986). The presumed cause of hepatitis is still unknown, since the vast majority of cases are seronegative for hepatotropic viruses like hepatitis A, B and C, GBV-C and other Flaviviridae (Hibbs JR *et al*, 1992; Brown KE *et al*, 1997; Safadi R *et al*, 2001). Clinical features and experimental results strongly suggest a central role for an immune-mediated pathogenesis. One of the possible mechanisms for HAA, as well as for idiopathic aplasia, is T-cell mediated suppression of bone marrow, and liver infiltration with activated CD8 cells (Lu J *et al*, 2004). Treatment protocols include allogeneic bone marrow transplantation (BMT) and combined immunosuppressive therapy (IS) when a suitable donor is lacking. Due to the rarity of the disease, reports on treatment results are scarce, contradicting and based on small numbers: a very poor prognosis has been described in early studies (Ajlouni K *et al*, 1974; De Planque MM *et al*, 1988; Najean Y *et al*, 1979), while others

1 show that treatment results in HAA are comparable to those obtained in other forms of acquired
2 aplastic anemia both with BMT and IS (Brown KE et al, 1997; Witherspoon RP et al, 1984; Kiem HP
3 et al, 1996; Locasciulli A et al, 1990; Osugi Y et al, 1978). The aim of the present study was to
4 analyse epidemiology and treatment results in a large European series of HAA reported to the
5 Severe Aplastic Anemia Registry of the EBMT - SAA Working Party since 1990. To better ascertain
6 prognosis in this particular form of marrow aplasia, we also compared treatment results to those
7 obtained in Idiopathic Aplastic Anemia patients referred to the Registry during the same time-period.
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14 **MATERIALS and METHODS**

15 **Design**

16 This retrospective cohort study used data provided by 257 centers from 29 Countries reporting to
17 the European Group for Blood and Marrow Transplantation (EBMT) Severe Aplastic Anemia
18 Working Party between 1990 and 2007. Collected data included year of treatment, month and
19 season of diagnosis as well as all variable related to the type and outcome of first line therapy:
20 pretreatment blood values, date, type, source and protocols for transplant group and date, type of
21 immunosuppressive therapy, lack of response to therapy, status at latest follow-up, causes of death,
22 type and date of late complications. Lack of response was identified by persistent transfusion
23 requirement. Follow-up was completed by September 2008.
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31 **Prevalence of HAA**

32 A total of 3916 patients with acquired aplastic anemia, diagnosed according to current criteria (
33 Camitta BM et al, 1978) were treated in Europe, between 1990 and 2007, and were reported to the
34 SAA-WP Registry. Hepatitis –associated aplastic anemia (HAA) accounted for 214 cases (5.4%).
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37 **Table 1** describes the prevalence of HAA in different countries.

38 **Treatment**. Table 2 describes demographic characteristics of patients with HAA, compared to non-
39 HAA patients.
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41 ***Immunosuppressive therapy***

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Non-HAA patients: 1485 patients with non- HAA received Immunosuppression (IS) as first line therapy. The median interval between diagnosis and treatment is 27 days (range 0-3956) . Neutrophil counts at the time of treatment were available in 1350 patients , and allowed for classification of AA as very severe (31%), severe (22%) and non severe (31%). Median follow-up at the time of analysis was 1911 days (range 0-6468) for patients surviving , and 382 days (range 1-5138) for deceased patients, respectively. IS therapy consisted on *anti-thymocyte globulin (ATG)* and Cyclosporin (*CyA*) in the majority of patients, regardless of etiology: *582 received ATG+CyA and 487 received ATG+CyA+ growth factor, 154 ATG alone.* Most patients received the horse formulation as first line therapy; rabbit ATG was used more rarely as first line, but commonly as second line therapy.

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Hepatitis associated aplastic anemia. A total of 75 patients with HAA received Immunosuppression as first line therapy: *31 received ATG+CyA , 24 received ATG+CyA+ growth factor and 9 ATG alone.* Median interval between diagnosis and IS was 10 days (range 0-3788).

23 **Bone Marrow Transplantation**

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Non-HAA patients. A total of 2217 patients with *non hepatitis associated aplasia*, received a BMT . The median interval from diagnosis to treatment was 108 days (1-5477) . The majority of patients were grafted from an HLA identical sibling (74%) , and received marrow as a stem cell source (70%)

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Hepatitis associated aplastic anemia. A total of 214 patients with HAA were allografted, most of them with marrow (82%) from an identical sibling (83%). Median interval between diagnosis and BMT was shorter than idiopathic AA (75 vs 108 days, $p=0.0001$) (range 12-2063).

36 **Statistical analysis**

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The students T and Mann Whitney tests were used for continuous variables , the Chi-square for 2x2 tables and the log-rank test for time dependent variables and Kaplan Meier curves were used for actuarial survival. A COX multivariate analysis was run separately on patients receiving first line IS or first line BMT, with survival as an end point: variables entered in the model were patient age, interval diagnosis-treatment (*cut off =median interval in days*), etiology of AA (and year of treatment. The number cruncher software (NCSS, version 5.0; JL Hintze, Kaysville, UT) was used to perform the analysis.

RESULTS

Prevalence of HAA . The average prevalence of HAA in Europe , between 1990 and 2007 , was 5.4%, and the median was 7% , with a range between 0% and 30%. Indeed, the distribution among Centers who registered aplastic anemia patients in this time period was not homogeneous, with prevalence peaks of HAA up to 15% (Table 1). However, we must consider that the Registry includes both large Centers providing more than 400 cases each, and others with only scattered registered patients per year (Table 1). There was no significant difference in distribution of both HAA and all the other acquired aplastic anemia according to month ($p > 0.1$) and year of diagnosis ($p = 0.6$). There was no causative virus for hepatitis in 94% of HAA patients; in 15 cases it was a hepatitis virus (6%): of these 9 were hepatitis B virus and 6 hepatitis A virus. The age at diagnosis was significantly younger in HAA patients: 15 (range 2-73) versus 20 years (range 1-94) in other acquired AA ($p < 0.01$) (Table 2). There was also a male prevalence in HAA (68% vs 58% , $p = 0.002$) (Table 2) .

Immunosuppression. The overall actuarial 10 year survival of all 1560 patients given 1st line IS therapy , is 68%: 69% for 75 HAA patients and 59% for 1485 non-HAA patients ($p = 0.5$) (Figure 1). Predictors of survival for IS patients in multivariate analysis were patients age , with a RR of 1.68 for patients over 20 years, a the interval diagnosis treatment, with a borderline RR of 1.2 for patients treated beyond 26 days from diagnosis ($p = 0.04$) (Table 3) . There was no effect of etiology (HAA vs non-HAA) and of year of IS treatment. Causes of death were similar in patients with HAA and idiopathic AA , and included no response (18% and 21%) , relapse (1% each) , secondary malignancy in (1.3 vs 1.4%) .

Of the original 1560 patients given 1st line IS, the proportion of patients requiring a second line transplant was identical in non-HAA and HAA patients: 29/75 (39%) vs 585/1485 (39%) ($p = 0.8$) , and survival comparable.

Bone Marrow Transplantation.

The actuarial 10 year survival of 2356 patients receiving 1st line BMT was 70% (56% for alternative donor BMT vs 75% for HLA identical sibling BMT). The median age of allografted patients was significantly younger in HAA (14 years , range 3-60) as compared to idiopathic AA (19 years, range 1-62): thus comparisons were made after stratification for age ($\leq / > 20$ years). Figure 2a shows actuarial survival for HAA patients ≤ 20 years of age , grafted from HLA identical siblings (88%) compared to idiopathic AA (82%) ($p = 0.3$). Figure 2b shows the same comparison for patients > 20 years of age: 69% vs 65% survival ($p = 0.8$) . The survival in patients grafted from alternative donors was also similar in HAA and idiopathic AA (69% vs 64%; $p = 0.7$).

In multivariate COX analysis , predictors of survival were younger age (RR 1.5 for patients older than 20 years) (Table 3), interval diagnosis-transplant (RR 1.8 for patients grafted beyond day 140) and year of transplant (RR 0.82 for patients grafted after 1998).

Peripheral blood (PB) transplants had overall inferior outcome as compared to bone marrow (BM) transplants (66% vs 72%, $p = 0.002$); this was true also after correcting for patient age (RR for BM vs IS 0.84, $p = 0.001$). The effect was seen both for idiopathic as well as HAA patients.

DISCUSSION

We have shown in this study that (a) the incidence of hepatitis associated aplasia (HAA) in the last 17 years is 5%, and seems to be homogeneously distributed over the years, months and geographic areas in Europe; (b) the outcome of Immunosuppression or bone marrow transplantation, is comparable to non-HAA patients, treated in the same period of time; (c) negative predictors of survival are patients age and delayed treatment for both idiopathic and HAA.

As to the first finding, epidemiology data on HAA are difficult to obtain, because aplastic anemia is a rare disease, and because published reports are often based on few cases. The present large series of HAA, includes 214 HAA patients out of 3916 patients with acquired aplastic anemia, diagnosed in Europe between 1990 and 2007. Our findings seem to confirm epidemiology data previously published. The average prevalence of HAA in Europe was 5%, and the median was 7% with a range from 0% to 15%. The distribution among the Centers who registered AA patients in this time period was not homogeneous. The highest prevalence peaks seem to concentrate in some Eastern European Countries, such Russia, Poland, Lituania, Belarious. Our data, however should be consider with caution. In fact, the number of AA patients registered varies widely, with 8 large Centers providing over 75% of all cases, while others included only scattered registered patients per year. These epidemiologic observations however should encourage further prospective studies. When analyzed according to the season of diagnosis, there was no significant difference in distribution of both HAA and all the other acquired AA according to month ($p > 0.1$) and year of diagnosis ($p = 0.8$). We therefore couldn't identify seasonal peaks or periods of outbreaks in this study. As to the clinical characteristics, HAA patients were younger (15 vs 20 years), and there was a higher prevalence of males (68% vs 58%) thus confirming previous observations (Brown KE *et al*, 1997). The presumed cause of hepatitis is still unknown, being the vaste majority of cases seronegative for hepatotropic viruses like hepatitis A, B and C, GBV-C and other Flaviridae (Hibbs JR *et al*, 1992; Brown KE *et al*, 1997; Safadi R *et al*, 2001). Indeed, in our cohort a possible hepatitis virus etiology was identified in only 15 cases (6%)

As to the second finding, treatment results were quite comparable in both groups, thus confirming that the prognosis of HAA does not differ from other acquired AA. Clinical features and experimental results strongly suggest a central role for an immune-mediated pathogenesis, for both HAA and idiopathic bone marrow failure. In HAA, T-cell mediated suppression of bone marrow may be associated with liver infiltration of activated CD8 cells (Lu J *et al*, 2004), thus causing increased transaminase levels and eventually jaundice. In this study, 75 HAA patients were treated with Immunosuppression as first-line therapy. 10 year survival was 69%. These results are comparable to those obtained in 1485 patients with acquired AA, and this was confirmed in a multivariate COX analysis, in which etiology has no prognostic effect on survival. The strongest negative predictor of survival was age, with a significantly higher risk of death for patients over 20 years. A longer interval between diagnosis and therapy was also associated with worse outcome, although this was less significant ($p=0.04$). This result, argues against delaying IS therapy for patients with HAA,

1 although some haematologists may believe that anti-thymocyte globulin should be delayed for
2 some time, usually until bilirubin and transaminase levels have normalized. Year of treatment had
3 no influence on outcome, suggesting that results of IS therapy have remained unchanged over the
4 past 17 years.
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8 Among 2356 transplants, results were also similar between HAA and non-HAA patients. Because
9 HAA patients are younger, survival was studied in two separate cohorts, less and over 20 years of
10 age: with this stratification survival was superimposable. This is confirmed in a multivariate COX
11 analysis, with age being the strongest negative predictor, followed by a longer interval between
12 diagnosis and transplant. **This is in keeping with the recent analysis on the EBMT risk score in
13 patients with aplastic anemia (Gratwohl A et al, 2009).** An overall improvement in outcome for
14 transplant patients, is shown in the COX analysis, with a relative risk of 0.82 for patients grafted
15 beyond 1998: this is probably due to improved supportive care, including new anti-infectious agents.
16 This study also confirms the negative impact of peripheral blood (PB) as a stem cell source as
17 compared to bone marrow (BM), and again this was true for HAA and idiopathic AA.
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24 In conclusion: HAA is reported in a small fraction of patients with acquired bone marrow
25 failure, and does not seem to show yearly or monthly variation over a long period of time. The
26 outcome of transplantation or immunosuppression are equally successful in HAA as they are in
27 idiopathic AA, and negative predictors are similar. In particular survival is reduced in patients with
28 longer interval between diagnosis and treatment, thus supporting an early intervention in all patients
29 with acquired AA.
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Appendix :Centers reporting patients to the EBMT Registry , and selected for this study

Hôpital Necker-Paris, Hôpital Timone-Enfants-Marseille, Leiden University Hospital-Leiden, Klinik fuer Innere Medizin III-Ulm, Imperial College-London, Rigshospitalet-Copenhagen, Hopital St. Louis-Paris, University Hospital Gasthuisberg-Leuven, University Hospital-Huddinge, Royal Free-London, Ospedale San Martino-Genova, Univ Children Hospital-Helsinki, Medizinische Universitaet-Wien, Western General Hospital-Edinburgh, Unité de transplantation et de thérapie cellulaire-Marseille, Hopital Jean Minjoz-Besancon, Hospital de la Princesa-Madrid, St Radboud-Nijmegen, Hosp. Reina Sofia-Córdoba, Erasmus MC-Daniel den Hoed-Rotterdam, Ospedale Civile-Pescara, Hôpital Henri Mondor-Creteil, Hotel Dieu-Nantes, The Oxford Radcliffe Hospital-Oxford, Div. Stem Cell Transplantation and Immunotherapy-Kiel, St. James Hospital Trinity College-Dublin, University Hospital-Essen, Hospital Santa Creu i Sant Pau-Barcelona, Service D'Hematologie-Geneva, Ospedale Maggiore di Milano-Milano, University Hospital-Uppsala, CHU Bordeaux-Pessac, Institute G. Gaslini-Genova, Ospedale San Gerardo-Monza, University Hospital-Lund, Clinica di Oncoematologia Pediatrica-Padova, Policlinico San Matteo-Pavia, Ospedale S. Camillo-Forlanini-Rome, Spedali Civili Brescia-Brescia, Hannover Medical University-Hannover, Hospital San Maurizio-Bolzano, University Hospital Center Rebro-Zagreb, Ospedale di Careggi-Firenze, Onco-Ematologia Pediatrica-Torino, Università Cattolica S. Cuore-Rome, Rambam Medical Center-Haifa, GATA BMT Center-Ankara, Institute of Clinical Immunology-Novosibirsk, Bristol Royal Hospital for Children-Bristol, Ospedale V. Cervello-Palermo, Royal Liverpool University Hospital-Liverpool, Helsinki University Central Hospital-Helsinki, University Hospital-Tübingen, Lower Silesian Centre for Cellular-Wroclaw, St. George's Hospital-London, IRCCS Policlinico San Matteo-Pavia, George Papanicolaou General Hospital-Thessaloniki, Civic Hospital-Noale, Paediatric Hemato Oncology & BMT-Tel-Hashomer, Hospital Carlos Haya-Málaga, University Children's Hospital-Graz, Manchester Royal Infirmary-Manchester, University Hospital Eppendorf-Hamburg, Ankara University Faculty of Medicine-Ankara, University of Ankara-Ankara, Ege University-Izmir, Hôpital Robert Debre-Paris, Poznan University of Medical Sciences-Poznan, Hospital Covadonga-Oviedo, Vilnius University Hospital Santariskiu Klinikos-Vilnius, Institute of Hematology and Blood Transfusion-Prague, Ospedale Bergamo-Bergamo, Centre Hospitalier Universitaire de Rennes-Rennes, Hospital Universitario La Fe-Valencia, Hopital d'Enfants, CHU de Dijon-Dijon, Hopital E. Herriot-Lyon, Silesian Medical Academy-Katowice, Pediatric University Teaching Hospital-Bratislava, Russian's Children's Hospital-Moscow, Centre Pierre et Marie Curie-Alger, SPb State I. Pavlov Medical University-St. Petersburg, Poznan University of Medical Sciences-Poznan, Umea University Hospital-Umeå, Hospital Universitario La Paz-Madrid, St. László Hospital-Budapest, University Hospital Gent-Gent, Chaim Sheba Medical Center-Tel-Hashomer, ICO – Hospital Duran i Reynals-Barcelona, Hospital Virgen del Rocío-Sevilla, Our Lady's Hospital for Sick Children-Dublin, North Trent BMT Programme (Adults)-Sheffield, Johannes-Gutenberg-University-Mainz, Ospedale A. Businco-Cagliari, S. Bortolo Hospital-Vicenza, Medical University of Gdansk-Gdansk, Hospital No. 9-MINSK, Hopital Debrousse-Lyon, Universitaetsklinikum Dresden-Dresden, University Hospital Erlangen-Erlangen, Università degli Studi di Cagliari-Cagliari, Centre Henri Becquerel-Rouen, H Hautepierre-Strasbourg.

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Table 1: PREVALENCE OF HEPATITIS ASSOCIATED APLASTIC ANEMIA (HAA) IN EUROPE, ACCORDING TO COUNTRIES, DIAGNOSED BETWEEN 1990 AND 2007

Distribution in Countries	Total patients	n.of	Total HAA	n. Of	% HAA
Russia	39		5		13
Greece	20		2		10
The Netherlands	142		5		4
Belgium	84		2		2
France	415		28		7
Spain	192		13		7
Hungary	48		1		2
Italy	496		34		7
Romania	1		0		0
Switzerland	86		4		5
Slovakia	25		2		8
Austria	52		2		4
United Kingdom	415		27		6
Denmark	30		2		7
Sweden	101		8		8
Norway	11		0		0
Poland	111		13		12
Germany	594		19		3
Turkey	53		3		5
Belarus	13		2		15
Algeria	90		2		2
Portugal	14		0		0
Ireland	45		3		7
Finland	37		3		8
Lithuania	3		1		33
Estonia	3		0		0
Serbia and Montenegro	14		0		0
Croatia	15		1		7
Slovenia	3		0		0
Israel	40		4		10
Czech Republic	49		2		4
Others	456		26		6
TOTAL	3702		214		6

TABLE 2: Clinical data of patients , according to etiology and treatment given

	HAA*	non-HAA	p
n. patients	214	3702	
Patient age :			
Median (range) years	15 (2-73)	20 (1-94)	0.00001
Interval Diagnosis-treatment			
Median (range) days	46 (1-3788)	62 (1-5477)	0.00001
Patient gender			
Male (%)	145 (68%)	2129 (58%)	0.002
Year of treatment			
Median (range)	1998 (90-07)	1998 (90-06)	0.8
Severity			
vSAA	31(41%)	459 (31%)	
SAA	12 (16%)	337 (22%)	
nSAA	19 (26%)	454 (31%)	
missing data	13 (17%)	235 (16%)	0.1
First line therapy			
IS /Transplant	75/139	1485/2217	0.1
Median follow up			
Surviving patients in days (range)	1506 (244-6317)	1385 (172-6291)	

Table 3. Cox Regression analysis of patients treated with immunosuppressive therapy (IS) or bone marrow transplantation

	Immunosuppression		Bone Marrow Transplantation	
	RR	P	RR	P
Age	1.68	.0000	1.52	.00001
Interval Dx-Tx	1.20	.04	1.89	.00001
Etiology Idiopathic/HAA	.29	.19	.19	.3
Year of treatment	.09	.37	.82	.03

Variables: **Age** : baseline value < 20 years; compared value =>20 years . **Interval Dx-Tx** (interval diagnosis treatment): baseline value =26 days for patients receiving first line immunosuppressive therapy (IS) and 140 days for patients receiving first line transplantation (BMT); **Etiology**: baseline value =idiopathic; compared value =hepatitis associated (HAA); **year of treatment**: baseline value <1998; compared value => 1998.

LEGEND FOR FIGURES

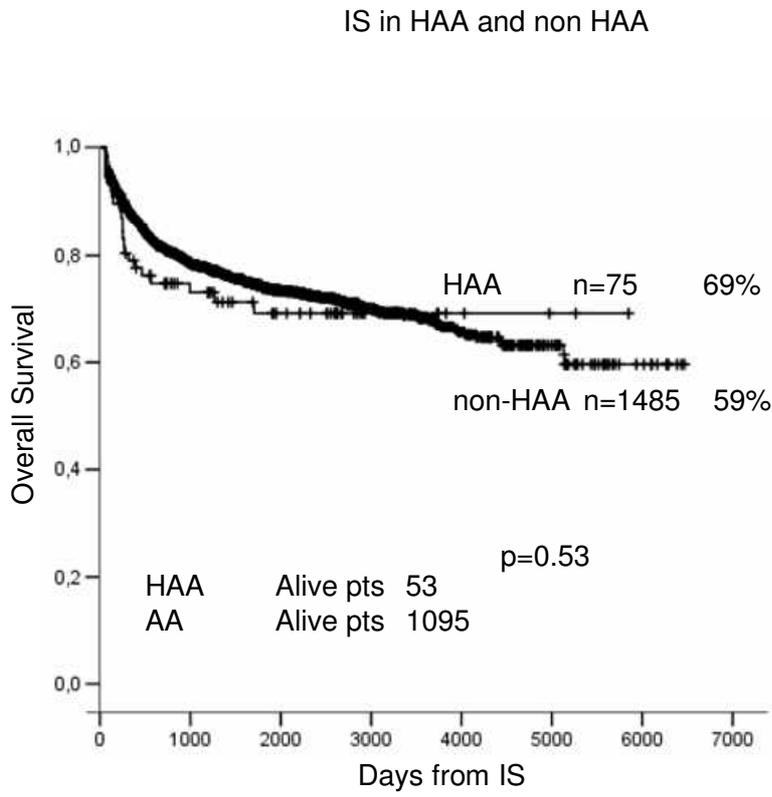
Figure 1: 10-year survival after IS in HAA and all other AA patients.

Figure 2a : Overall survival after HBMT from HLA id. sib. in patients under 20 years for HAA and all other AA patients at 10 year follow-up.

Figure 2b: Overall survival after HBMT from HLA id. sib. in patients over 20 years for HAA and all other AA patients.

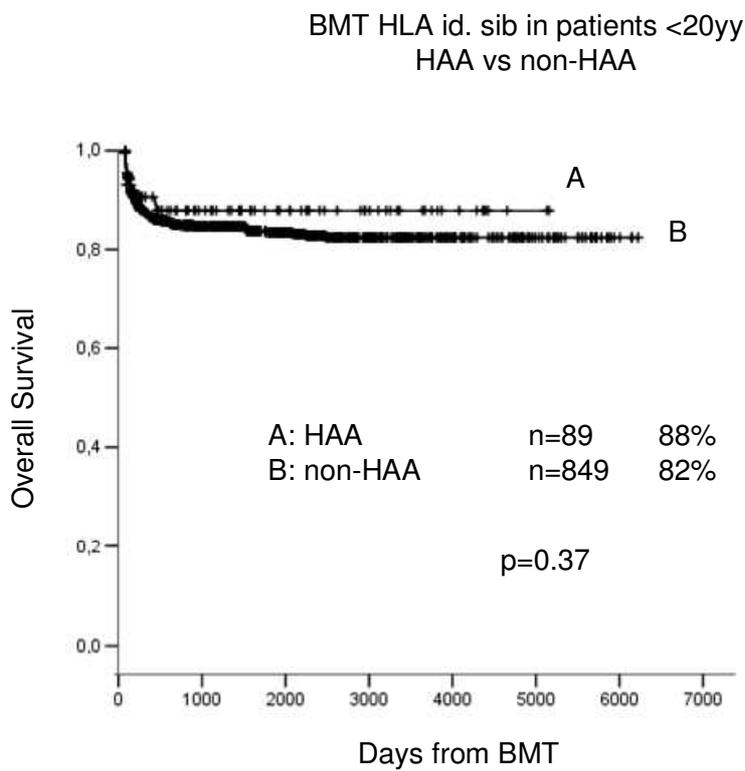
For Peer Review

Figure 1



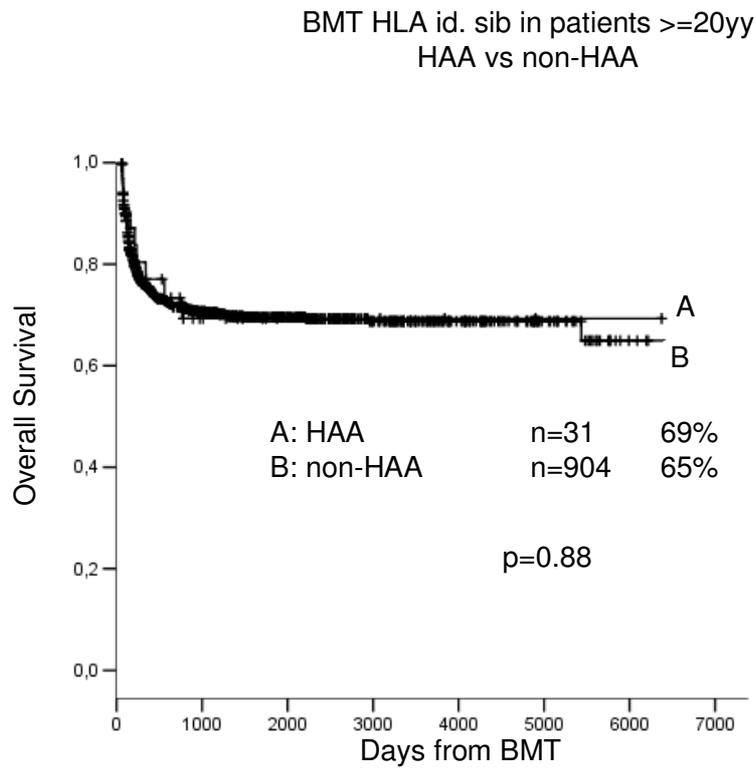
Review

Figure 2a



Review

Figure 2b



Review