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1. ARTICLE TITLE:

Physical health conditions and quality of life in adults with primary immune deficiency diagnosed during childhood: a CEREDIH study.

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2. Abstract

Background: Most children with primary immune deficiency (PID) now reach adulthood. However, few studies have evaluated their health status and health related quality of life (HRQoL).

Objective: To investigate long-term morbidity, the French Reference Center for PIDs initiated a prospective multicenter cohort: the F-CILC (French Childhood Immune deficiency Long-term Cohort). The data collected was used to assess the physical health condition of patients who reached adulthood and the impact on their quality of life.

Methods: Patients were asked to complete health status questionnaires. A severity score (grade1 ["mild"] to grade 4 ["life-threatening"]) was assigned to each health condition. The HRQoL of patients was compared to age- and sex-matched French normal values using the SF36 HRQoL questionnaire.

Results: Among 329 participants, the mean age at evaluation was 27.6 years with a 21-year mean follow-up after diagnosis, 43% reported at least one grade 4 health condition and 86% reported at least one grade 3 (severe) or 4 health condition. Twenty-five patients (7.6%) had been treated for cancer. Compared with the French norms, adults with PID scored significantly lower for all HRQoL domains. HRQoL was strongly associated with the burden of health conditions. The association with grade 4 or grade 3-4 health conditions was highly significant for all physical and mental domains.

Conclusion: Adults with PID diagnosed during childhood experienced a heavy burden of health conditions, which affected their HRQoL. Our results emphasize the need to closely monitor this vulnerable population.

3. **Clinical Implications:** We quantified the magnitude of health conditions in adults with PID diagnosed during childhood, emphasizing the need to closely monitor this vulnerable population and to use multidisciplinary health care teams.

4. **Capsule summary.** This is the first study of adult survivors of childhood PID describing how the burden of health conditions affect their quality of life. Our results emphasize the need to closely monitor this vulnerable population.
5. **Keywords.** primary immunodeficiency, childhood, young adults, health status, quality of life

6. **Abbreviations:**

PIDs: Primary immune deficiencies

CEREDIH: French Reference Center for PIDs

F-CILC: French Childhood Immune deficiency Long-term Cohort

F-CILSG: French Childhood Immune deficiency Long-term Study Group

HR-QOL: Health Related Quality of Life

HSCT: Hematopoietic Stem Cell Transplantation

CTCAE: Common Terminology Criteria for Adverse Events

ENT: Ear, Nose, and Throat

INTRODUCTION

Primary immunodeficiencies (PIDs) consist of a growing group of intrinsic errors of the immune system that induce higher susceptibility to recurrent infections, autoimmunity, allergy, cancer and other manifestations of immune dysregulation¹. PIDs comprise at least 300 genetically defined single-gene inborn errors of immunity¹. Although an increasing number of patients are diagnosed with adulthood onset PID, most of them are still diagnosed during childhood. Many patients require life-long therapy, either antibiotic or antifungal prophylaxis or immunoglobulin replacement therapy^{2,3}. Hematopoietic stem cell transplantation (HSCT) remains the only definitive cure for severe PIDs, although gene therapy has emerged as an alternative option for a currently limited and selected number of PIDs^{4,5}.

Actually, PIDs are an ontological framework characterized by high clinical, biological, genetic and therapeutic heterogeneity. Taken as a whole, they represent a vast group of conditions that are chronic, life-long serious and likely to affect life expectancy⁶. As survival is often considered the most important outcome in study designs, few studies have assessed the severity of health conditions. Previous reports have focused on either specific diseases⁷ or specific complications concerning transplanted SCID survivors⁸. In terms of HRQOL, most studies have focused on immunoglobulin replacement, investigating its effect on infection rates and patient well-being^{9, 10}.

The purpose of our study was to gain insight into how PIDs might affect patient health status by focusing on adults with PID diagnosed during childhood. Thus, we used the French Reference Center for PIDs (CEREDIH, www.ceredih.fr) national registry and the nationwide network of clinicians (both pediatricians and

adult physicians, who are all trained in the management of patients with PIDs and work in University teaching hospitals)¹¹. The CEREDIH, which was established in France in 2005, runs a large national PID registry with a current minimal prevalence of 7.10^{-5} inhabitants in the French population (see: www.ceredih.fr, last accessed: 01/10/2016)¹². Hereby we investigate 329 adults diagnosed during childhood with a PID and enrolled in a national survey with 889 participants (560 children and 329 adults). We address the prevalence and the severity of health conditions and their impact on quality of life.

METHODS

Study cohort.

The French Childhood Immune deficiency Long-Term Study Group (F-CILSG) is a CEREDIH working party which conducts a multicenter prospective follow-up program enrolling participants who met all of the following criteria: (1) patient with a PID included in the CEREDIH registry, (2) clinical diagnosis of PID before 18 years of age, (3) alive and living in France, and (4) individual who provided written informed consent to participate in the study. Contact and recruitment of eligible participants, using a uniform procedure, began in August 2013. The F-CILC questionnaires (along with a cover letter explaining the objectives of the study), study information documents and informed consent forms were sent via postal mail to all eligible French patients. When the questionnaire was not returned within three weeks' time, a trained interviewer contacted the patient by telephone to both verify that the questionnaire had been received and attempt to secure participation. Completed questionnaires received at the coordinating center were computerized according to the F-CILSG protocol. Patients were considered as a "participant" when the questionnaire was completed and returned along with the written informed consent document signed by the patient. Patients were considered as "lost to follow-up" after extensive efforts failed to locate them. Patients were considered as "non-participant" when either they declined participation verbally via telephone or in writing, or they indicated their willingness to participate but failed to return a completed questionnaire and signed informed consent document.

The study was financed by the French National Programme for Clinical Research (PHRC, Ministry of Health, EudraCT trial number 2012-A0033-35)

and has been approved by a review board (Comité National Informatique et Libertés, CNIL). We received written consent from all participants included in our study. The Local Ethics Committee (Comité de Protection des Personnes Sud-Méditerranée V, France: trial number 12.024) and the Comité Consultatif sur le Traitement de l'Information de Recherche dans la Santé (CCTIRS trial number 12.681) approved this study.

Assessment of patient PID

Information concerning demographic data, clinical and genetic PID diagnosis, date of onset of PID symptoms, date of clinical diagnosis of PID, therapy history data (particularly Ig replacement and HSCT) and a set of clinical laboratory results were obtained from the CEREDIH registry, which was updated on an annual basis.

According to the criteria of the International Union of Immunological Society (IUIS), PIDs were classified into six subgroups: predominantly T cell deficiencies, predominantly antibody deficiencies, phagocytic disorders, immune dysregulation (i.e., Familial Hemophagocytic Lymphohistiocytosis, IPEX syndrome), other well-defined PIDs and complement deficiencies¹.

Assessment of health conditions

Participants completed the adult F-CILC questionnaire. This self-administered questionnaire, which was printed in French, included 638 items covering the following domains: socio-demographic characteristics (such as education, employment, marital condition), PID diagnosis and family history, medical care practices (e.g., Ig replacement, HSCT), transition to adulthood care facilities, and physical health condition (e.g., cardiac, respiratory, ENT, gastrointestinal, dermatological, genitourinary, musculoskeletal, neurological, endocrinopathy,

surgery and malignancy). The 320 items concerning physical health conditions were based on the questionnaire previously published for the Cancer Childhood Survivor Study (CCSS) and then adapted to the PID context. It has been successfully used to describe chronic health conditions in childhood cancer survivors, thereby confirming that patients are able to accurately report the occurrence of adverse medical conditions^{13, 14}.

Each health condition was self-rated by the patient according to the four-grade scale: grade 1 = mild, grade 2 = moderate, grade 3 = severe, grade 4 = life-threatening/disabling.

To avoid under-grading, a medical evaluation of each health condition was also performed, and the higher of the two grades was selected for the final evaluation. Medical grading was performed applying the Common Terminology Criteria for Adverse Events (CTCAE) v3.0: grade 1 = mild, grade 2 = moderate, grade 3 = severe, grade 4 = life-threatening/disabling ("grade 5 = death" was not applicable in this study)¹⁵. When a particular condition was not listed (e.g., aspergillosis, pneumocystosis) a multidisciplinary group assessed the severity based on the four-grade scale. In situations when we were unable to distinguish between the four grades due to lack of information, the lower score was selected.

Assessment of health-related quality of Life (HRQoL)

All patients were asked to complete the SF-36 questionnaire, a reliable instrument used to assess self-perceived health status in adults¹⁶. The SF-36 is comprised of 36 items describing eight dimensions: physical functioning, social functioning, role limitations due to physical health problems, role limitations due to emotional problems, general mental health, vitality, bodily pain and general

health perceptions. Two summary composite scores were then generated, the physical composite score and the mental composite score. All scores ranged between 0 and 100, with higher scores indicating better HRQOL. The French general population reference values are available for gender- and age-matched comparison purposes¹⁷.

Statistical analyses

We determined the prevalence and severity of physical health conditions by using two endpoints:

- Life-threatening/disabling (grade 4), reported either by the patient or via medical assessment (according to CTCAE score)
- Severe or life-threatening/disabling (grade 3-4), reported either by the patient or via medical assessment

These two events have been used throughout the analysis.

Statistical analyses were performed using SPSS version 20.0 (SPSS Inc. Chicago, IL, USA). The data are expressed as number and percentage or mean $\pm$ standard error of mean (SEM). The paired student t-test was used to compare the SF-36 mean scores reported by patients with those obtained for age-matched and sex-matched French control subjects. All quantitative variables were compared using the Student t-test, ANOVA or Kruskal-Wallis non-parametric test as appropriate. The significance threshold was set as $p < 0.05$.

Results

Patient characteristics

Between 06/01/2013 and 12/31/2014, 1561 patients identified in collaborating CEREDIH institutions were contacted (Supplemental **Figure E1**). A completed questionnaire and a signed informed consent were obtained for 889 (56%) participants. We observed no significant difference between patients included in the F-CILC and eligible patients who were not included, with regard to gender, PID diagnosis, age at PID diagnosis and age at study participation.

Among the 889 participants, 329 were adults over 18 years of age and all were included in the following analyses. **Table 1** displays the characteristics of these 329 adult patients. Mean age at PID diagnosis and at the time of the study were 6.6 ± 0.47 years and 27.6 ± 0.49 years, respectively. The mean interval from date of PID diagnosis to date of completion of the questionnaire was 20.9 years. Of the 329 adult participants, 58 (17.6%) had undergone HSCT as part of the PID treatment. A total of 142 patients received Ig replacement (including 11 patients with HSCT), administered either intravenously (46% patients) or subcutaneously (54% patients). Sixty-five percent of patients underwent therapy at home, and 80% were the principal decision makers when choosing replacement therapy. Regarding access to adult healthcare, 87% of patients were followed by an immunologist, while 16% were monitored by a pediatrician. Of the 55 adults who continued to be followed by their pediatrician, the majority (83%) wished to delay the transition to adult healthcare and 15 patients had received HSCT. Among the 269 patients currently followed by the adult team, 86% were satisfied with their transition. During the past year, the consultation frequency was quarterly,

biannually and annual in 22.5%, 33% and 27% of patients, respectively. Finally, during the same period, 90 patients were hospitalized, two thirds once.

Health condition outcomes

Supplemental **Figure E2** summarizes all health conditions reported by participants. Forty-three percent experienced at least one grade 4 (life-threatening/disabling) health condition. The percentage of patients with 1, 2, 3, 4 and 5 or more grade 4 health conditions was 23.1%, 9.1%, 5.5%, 2.7% and 2.7%, respectively.

Eighty-six percent of patients experienced at least one grade 3 (severe) or grade 4 health condition. The percentage of patients with 1, 2, 3, 4 and 5 or more grade 3-4 health conditions was 18.5%, 18.2%, 15.5%, 12.0% and 21.2%, respectively.

Figure 1 shows the frequency of the different health conditions according to the following categories: respiratory system, ENT, gastro-intestinal, oral, genitor-urinary, neurological, musculoskeletal, surgery, malignancy, dermatological, cardiac and endocrine. The most frequent grade 4 health conditions involved 3 categories, surgery (20%, 95%CI: 15.7-24.6), respiratory (10%, 95%CI: 6.6-13.2) and intestinal (9%, 95%CI: 6.3-12.9). The bulk of grade 3 or 4 health conditions involved the following 8 categories: surgery (49.5%, 95%CI: 44-55), respiratory (43%, 95%CI: 37.5-48.4), ENT (36%, 95%CI: 31.1-40.9), intestinal (34%, 95%CI: 29-37.5), dermatological (24%, 95%CI: 19.6-29.1), oral (19%, 95%CI: 15.1-23.9), neurological (18.5%, 95%CI: 14.9-23.6) and musculoskeletal (18%, 95%CI: 14.6-23.3). Furthermore, 7.6% of the patients reported a malignancy, including lymphoma (n=13), leukemia (n=3), skin malignancies (basal cell carcinoma=2,

melanoma=1), breast cancer (n=1), bowel cancer (n=2), bone tumor (n=2) and brain tumor (n=1). Almost 50% of participants report a grade 3-4 surgery among which splenectomy, surgical drainage of an abscess, lobectomy, cardiac surgery, appendectomy, and ENT surgery.

Quality of life

Among 329 participants, 309 completed the SF36 questionnaire. Overall, PID had a strong negative impact on both physical and mental domains of quality of life in these adults. As reported in **Table 2**, when compared to the French population norms, adults with PID scored significantly lower for all domains of HRQOL.

According to the PID diagnosis (**Table 3**), no significant difference was observed in the physical or mental composite scores. Furthermore, no significant difference was observed in most subscales, with the exception of mental health subscale (higher scores were reported for immune regulation diseases and predominantly antibody disorders) and general health subscale (a better perception in combined immunodeficiency and immune regulation diseases).

Table 4 shows HRQOL according to whether or not the patient had received HSCT. Although the mental composite scores were comparable, there was a significant difference in the physical composite score and the general health subscale, which displayed a significantly higher score in the transplanted group.

Otherwise, quality of life was significantly diminished when hospitalization occurred during the past year (Supplemental **Table E1**). Conversely, HRQOL was not affected by the current prophylactic therapy (Ig replacement and

antimicrobial therapy versus none) or the duration of the disease (Supplemental **Tables E2 to E5**).

Quality of life outcome was strongly associated with the number of health conditions experienced by the patient. When only grade 4 health conditions were considered, the association was highly significant for both physical and mental composite scores as well as for all respective subscales. Patients who had experienced at least one grade 4 health condition were more likely to report poor HRQOL than patients who did not, and the scores were even lower with at least two health conditions (**Figure 2**). The same association was found for patients with grade 3 or 4 health conditions (**Figure 3**). However, as shown in Figures 2 and 3, the threshold for a poor quality of life appeared rather to be at least two health conditions.

DISCUSSION

The F-CILSG is a CEREDIH working party that conducts a multicenter prospective follow-up program addressing the long-term health outcomes of patients with PID. In this report, we focused on health conditions in 329 adults who had a diagnosis of PID during childhood, with a mean interval between diagnosis and study evaluation of 20.3 years. The severity of each health condition was evaluated using a four-grade scoring system according to both patient self-perception and the CTCAE.

To our knowledge, this is the first study to describe the health conditions of adult patients with a PID diagnosed during childhood at a population level. We show that the prevalence of severe or life-threatening health conditions is very high in adults with PID, particularly concerning surgery, respiratory, gastrointestinal, ENT and dermatological conditions. Only less than 15% of adults with PID had never experienced severe or life-threatening conditions. Additionally, these patients were more likely to have multiple conditions. We also found that prevalence of cancer was markedly raised considering the young age of our population. Finally, this heavy burden of health conditions markedly impacted patient quality of life compared with the general population. There are several limitations to keep in mind when interpreting these findings. First, our response rate (329/647 adults) raises the question of representativeness of our cohort, especially as we could not compare the two groups regarding socio-economical level, marital status or educational level, due to the lack of information regarding the non-participating population. Furthermore, the conditions were self-reported without external verification, with the exception of malignancy. Additionally, our list of conditions was not

exhaustive, especially for mental health, and some conditions that remain clinically silent might have been underreported. Furthermore, no data were collected concerning recent occurrences of acute stress, which have been shown to impact HRQOL. It is important to note however that the use of self-reported questionnaires has been shown to be a very accurate method in other comparable settings, such as children with malignancy in the CCSS^{13, 14}.

Some studies have assessed the frequency and severity of health conditions in subgroup of PIDs, such as SCID or chronic granulomatous disease^{7, 8} in children and agammaglobulinemia or CVID^{18, 19} in adults. In the largest cohort of CVID published and registered in the ESID registry (www.esid.org), Gathmann et al. have reported a clinical description of 2212 adults with CVID (including proportion of chronic complications and some self-reported outcomes) without assessment of severity¹⁸. Recently, in a survey conducted by the Immune Deficiency Foundation, Seeborg et al. have reported the perceived health among patients with PID, in which 39% of the patients perceived their health status as fair/very poor²⁰.

While few studies have assessed the severity of health conditions in PID patients, many studies have been carried out to evaluate the HRQoL among adults with PID, although almost exclusively in patients receiving chronic Ig replacement therapy^{10, 21, 22}.

In our study, we detected statistically significant impairments in all domains of quality of life in adults with PID. Moreover, we specifically assessed the impact of health condition burden on HRQoL and found a highly significant decrease in all composite scores and subscales in patients who experienced additional health conditions. Notably, we did not detect major differences in HRQOL

domains when comparing patients according to PID diagnosis, except among patients with immune dysregulation, who displayed high scores in mental health and general health. However, this may merely reflect a low statistical power of comparison due to the relatively small patient number in each diagnosis subgroup. Duration of disease did not affect patient quality of life, unlike recent hospitalization events, which suggests that the self-reported HRQoL is probably strongly influenced by recent events.

Interestingly, patients who underwent HSCT scored significantly higher with respect to general health and physical composite score, thereby suggesting that the post-HSCT group had a better HRQoL than the non-transplanted group. This observation appears quite unexpected, as PID transplanted cases are more severe than the non-transplanted cases. However, this feature should be interpreted with caution, as it may only reflect the curative potential of HSCT.

The significant impairment of HRQoL described in our PID cohort has also been reported in other patients suffering from severe chronic childhood disease who reached adulthood. Notably, this has been described in cystic fibrosis, juvenile chronic arthritis and in type 1 diabetes patients²³⁻²⁸.

In conclusion, our results quantify the magnitude of health conditions in adults living with PID diagnosed during childhood. Our findings clearly emphasize the need to closely monitor this vulnerable population and the importance of multidisciplinary health care teams.

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AUTHORSHIP CONTRIBUTIONS

VB, NM, PA, GM and AF designed the research study, performed the research, analyzed the data and wrote the manuscript. CV performed the statistical analyses. IP, FP, MA and CB performed the research and contributed to manuscript redaction. FP, MP, EJ, NA, NS, CT, VG, FM, PL, SB and CP contributed to the research and revised the manuscript.

CONFLICT OF INTEREST DISCLOSURES

No conflict of interest to disclose.

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Table 1: Patient characteristics (n=329)

	n (%) or mean $\pm$ SEM, years	
Gender	<i>male</i>	196 (59.6%)
Age at diagnosis		6.62 $\pm$ 0.47
HSCT	Yes	58 (17.6%)
PID diagnosis	Total n (%)	n with HSCT
<i>Predominantly antibody disorders</i>	143 (43.5%)	2
<i>Phagocytic disorders</i>	76 (23.1%)	9
<i>Combined immunodeficiencies</i>	37 (11.2%)	28
<i>Other well-defined PIDs</i>	36 (10.9%)	10
<i>Diseases of immune dysregulation</i>	28 (8.5%)	9
<i>Complement deficiencies</i>	5 (1.5%)	0
<i>Defects in innate immunity</i>	4 (1.2%)	0
Age at study participation (n=329)		27.59 $\pm$ 0.49
Interval between diagnosis and study (n=329)		20.33 $\pm$ 0.56
Interval between HSCT and study (n=58)		20.00 $\pm$ 1.26
Hospitalization during past 12 months (n=323)	Yes	90 (27.4%)
Current prophylactic therapy	None	93
<i>Regular Ig</i>	Yes	142
<i>Prophylactic antimicrobials</i>	Yes	175
<i>Both</i>	Yes	81
Physician specialty	<i>Immunology</i>	289
	<i>Other</i>	40

Table 2: Quality of life: comparison of patients with the general population

		Patients n=329	Reference group*	P-value
	n	mean $\pm$ SEM	mean $\pm$ SEM	
Physical functioning	300	84.93 $\pm$ 1.34	94.58 $\pm$ 0.17	< 0.001
Social functioning	299	72.12 $\pm$ 1.51	85.24 $\pm$ 0.22	< 0.001
Role: physical	290	68.93 $\pm$ 2.34	90.97 $\pm$ 0.23	< 0.001
Role: emotional	287	57.08 $\pm$ 1.90	88.28 $\pm$ 0.26	< 0.001
Mental health	295	66.39 $\pm$ 1.11	69.88 $\pm$ 0.18	0.002
Vitality	293	52.50 $\pm$ 1.18	63.76 $\pm$ 0.18	< 0.001
Bodily pain	295	72.61 $\pm$ 1.51	82.27 $\pm$ 0.23	< 0.001
General health	293	47.49 $\pm$ 1.43	76.26 $\pm$ 0.25	< 0.001
Physical composite	277	48.39 $\pm$ 0.18	54.47 $\pm$ 0.09	< 0.001
Mental composite	277	43.27 $\pm$ 0.57	48.39 $\pm$ 0.11	< 0.001

*Paired student t-test was used to compare the SF-36 mean scores reported by patients with those obtained for age-matched and sex-matched French control subjects

1 **Table 3:** Quality of life according to PID diagnosis

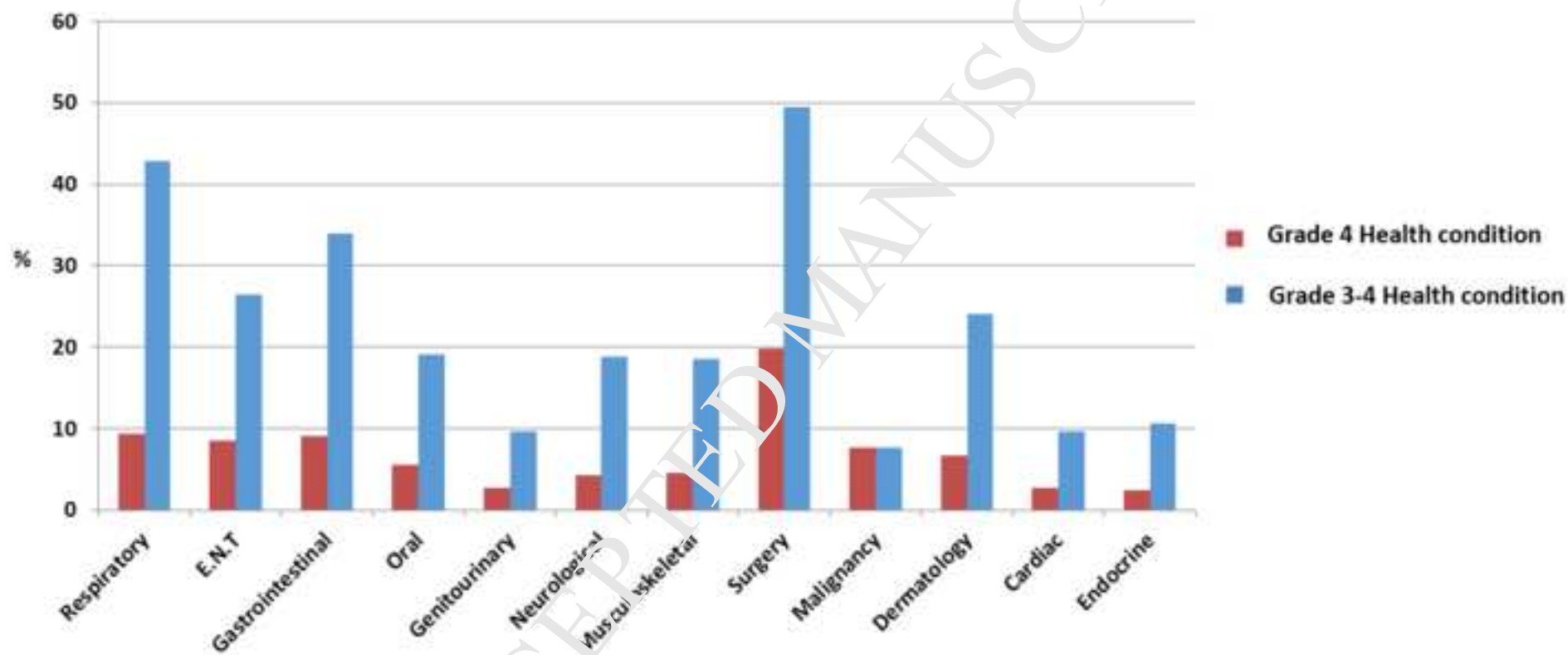
	PID diagnosis					
	Combined Immunodeficiencies n=37	Diseases of immune dysregulation n=28	Other Well- defined PIDs n=36	Phagocytic disorders n=76	Predominantly antibody disorders n=143	p-value
Physical functioning	82.08 ± 4.32	85.08 ± 5.07	81.92 ± 4.61	86.03 ± 2.32	85.04 ± 1.96	0.913
Social functioning	69.64 ± 4.76	79.91 ± 4.38	70.36 ± 4.20	68.40 ± 3.19	72.99 ± 2.17	0.362
Role: physical	71.57 ± 6.72	64.81 ± 8.25	78.13 ± 6.22	61.96 ± 4.94	69.78 ± 3.32	0.386
Role: emotional	56.86 ± 5.54	55.56 ± 5.63	54.94 ± 5.90	56.19 ± 3.41	57.43 ± 2.84	0.977
Mental health	65.26 ± 3.25	71.50 ± 3.52	60.82 ± 3.44	61.84 ± 2.28	68.67 ± 1.56	0.015
Vitality	53.21 ± 3.41	54.91 ± 4.40	50.62 ± 3.70	50.67 ± 2.20	53.50 ± 1.77	0.777
Bodily pain	72.97 ± 5.22	76.21 ± 4.97	75.50 ± 3.61	69.63 ± 3.04	71.64 ± 2.25	0.694
General health	57.57 ± 5.34	57.18 ± 5.40	44.91 ± 3.75	44.98 ± 2.7	45.05 ± 1.91	0.043
Physical composite score	49.95 ± 2.09	48.78 ± 2.16	50.89 ± 1.32	47.83 ± 1.09	47.45 ± 0.79	0.143
Mental composite score	42.96 ± 1.72	45.45 ± 1.55	41.25 ± 1.98	41.84 ± 1.05	43.81 ± 0.86	0.161

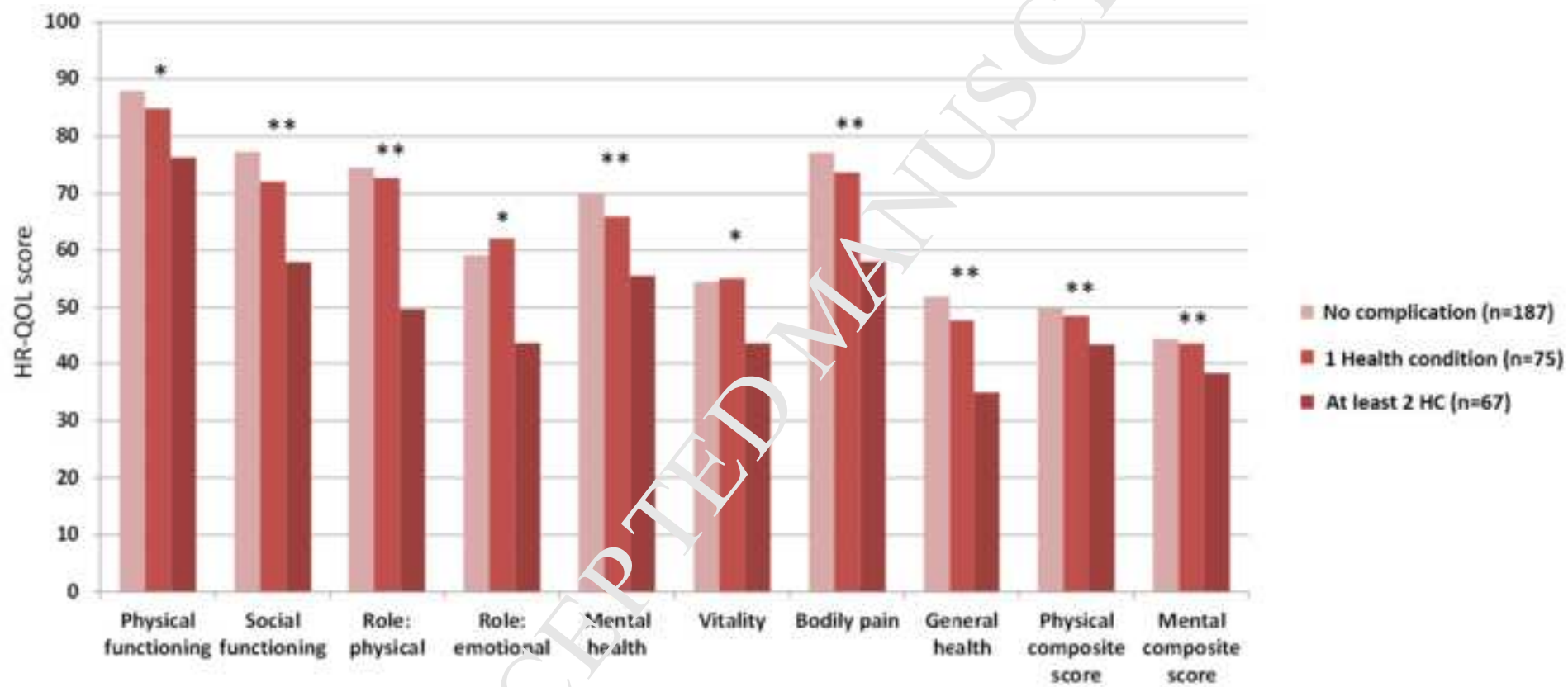
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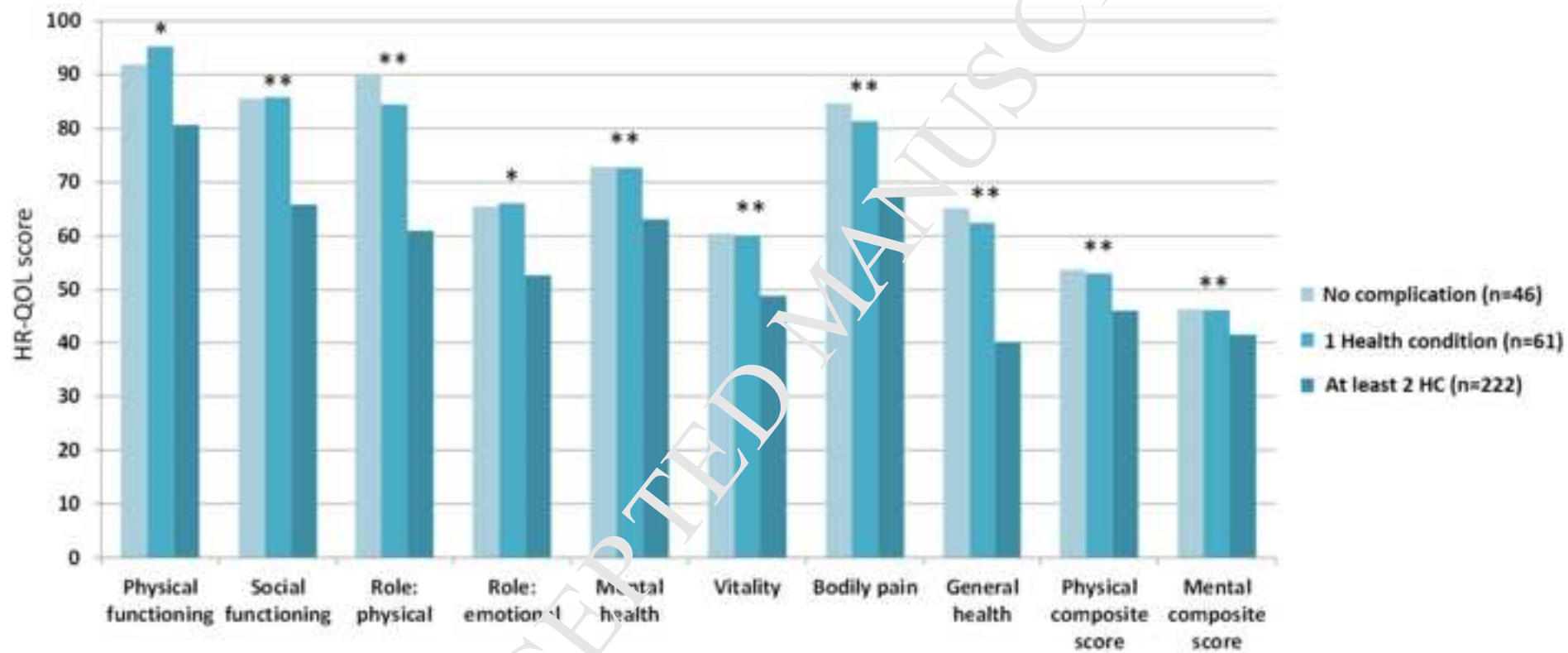
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Table 4: Quality of life according to whether or not the patient had received HSCT.

	HSCT		
	No n=270	Yes n=58	P-value
Physical functioning	85.53 ± 1.38	81.64 ± 3.59	0.252
Social functioning	71.83 ± 1.6	74.12 ± 3.5	0.547
Role: physical	67.90 ± 2.50	76.04 ± 4.99	0.148
Role: emotional	57.54 ± 1.99	53.51 ± 4.15	0.384
Mental health	66.66 ± 1.17	63.99 ± 2.63	0.345
Vitality	52.25 ± 1.27	53.61 ± 2.70	0.655
Bodily pain	71.90 ± 1.59	74.80 ± 3.68	0.450
General health	44.94 ± 1.41	60.62 ± 3.85	<0.001
Physical composite score	47.87 ± 0.58	51.09 ± 1.40	0.024
Mental composite score	43.22 ± 0.61	42.92 ± 1.28	0.840







Supplementary material

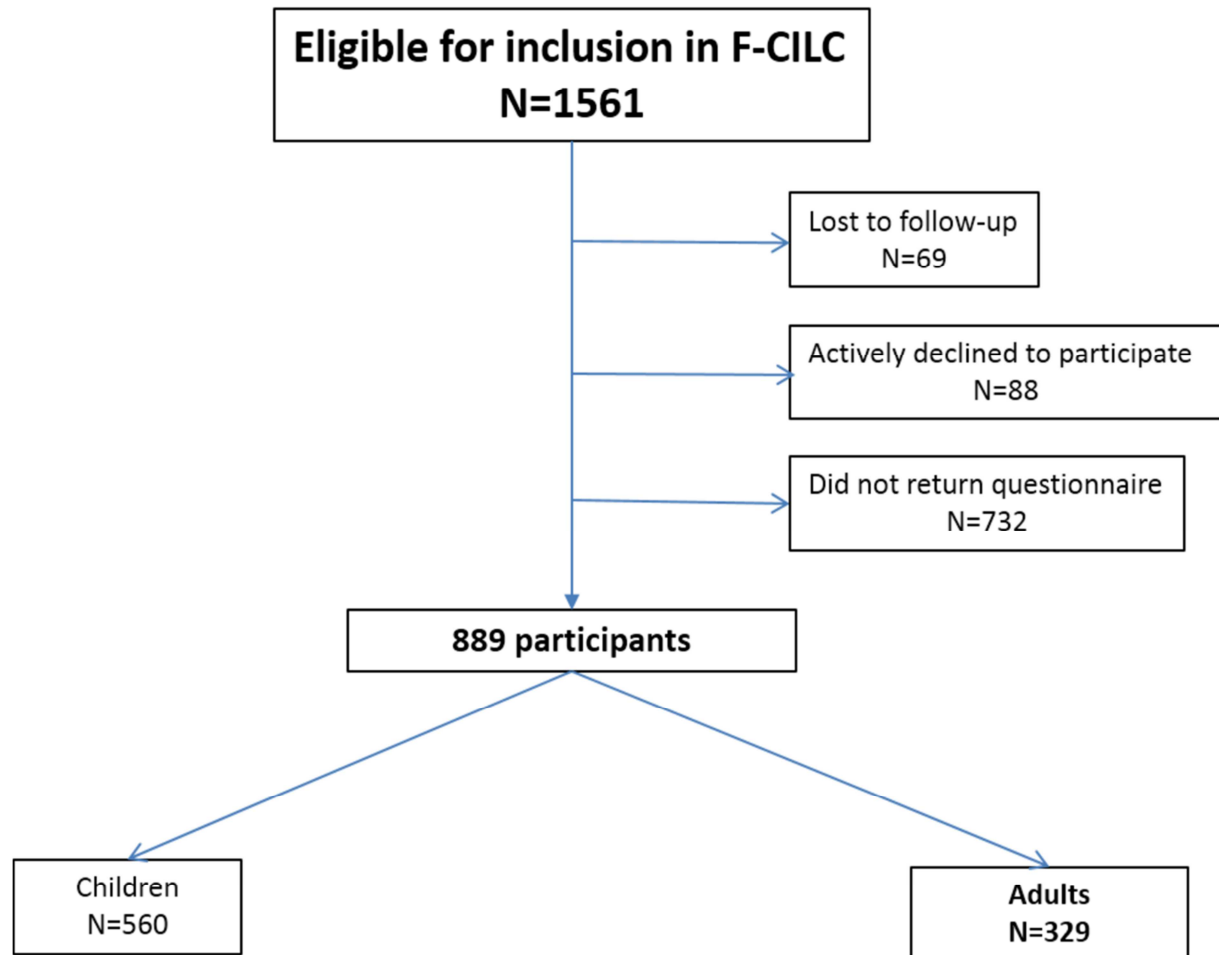
Figure E1: Flow chart, status of patients registered in the F-CILC (June 2015)

Figure E2: Burden of health conditions reported by adults with PID diagnosed during childhood. Percentage of adults with grade 4 (•) or grade 3-4 (•) health conditions.

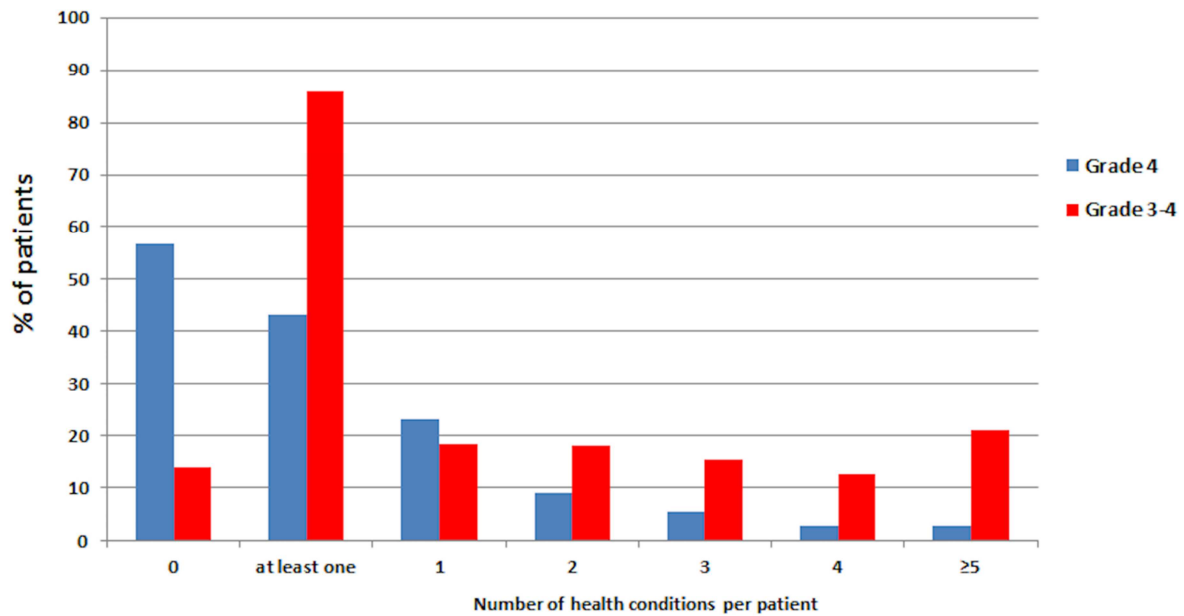


Table E1: Quality of life according to whether patients had been hospitalized in the past year (n=90) or not (n=239)

	Yes mean ± sem	No mean ± sem	P-value
Physical functioning	79.04 ± 2.75	87.30 ± 1.46	0.009
Social functioning	61.65 ± 2.85	76.64 ± 1.61	< 0.001
Role: physical	54.17 ± 4.60	75.71 ± 2.45	< 0.001
Role: emotional	47.87 ± 3.58	60.65 ± 2.05	0.002
Mental health	60.53 ± 2.07	68.83 ± 1.22	< 0.001
Vitality	44.43 ± 2.09	55.83 ± 1.32	< 0.001
Bodily pain	62.68 ± 2.94	77.01 ± 1.60	< 0.001
General health	37.23 ± 2.35	51.98 ± 1.62	< 0.001
Physical composite score	44.79 ± 1.09	49.98 ± 0.60	< 0.001
Mental composite score	39.54 ± 1.06	44.66 ± 0.62	< 0.001

Table E2: Median number of grade 4 or grade 3-4 health condition (HC) per patients in 271 patients without HSCT, according to median time between diagnosis and the study

	Median nb of HC grade 4/patient	p value	Median nb of HC grade 3-4/patient	p value
≤19.45	0.58 ± 0.11	0.054	2.60 ± 0.19	0.113
>19.45	0.90 ± 0.13		3.05 ± 0.21	

Table E3: Quality of life according to the median time between diagnosis and study (n=271; median time=19.45 years)

	≤19.45 years	>19.45 years	p value
Physical functioning	85.93 ± 2.19	88.66 ± 1.63	0.321
Social functioning	73.92 ± 2.36	70.30 ± 2.75	0.317
Role: physical	72.67 ± 38.94	63.92 ± 40.08	0.119
Role: emotional	58.42 ± 3.28	59.17 ± 3.15	0.869
Mental health	69.52 ± 1.58	66.80 ± 2.02	0.289
Vitality	53.21 ± 2.03	53.15 ± 2.07	0.984
Bodily pain	74.80 ± 2.45	69.33 ± 2.62	0.129
General health	47.58 ± 2.36	42.32 ± 2.19	0.104
Physical composite score	48.78 ± 0.95	47.19 ± 0.87	0.215
Mental composite score	44.08 ± 0.89	43.20 ± 1.04	0.525

Table E4: Median number of grade 4 or grade 3-4 HC /patients in 271 patients without HSCT, according to interquartile time between diagnosis and the study

	Median nb of HC grade 4/patient	p value	Median nb of HC grade 3-4/patient	p value
≤ 12.44	0.52 ± 0.13	0.244	2.54 ± 0.27	0.143
]12.44 - 19.45]	0.63 ± 0.18		2.65 ± 0.28	
]19.45 - 25.75]	0.84 ± 0.18		2.71 ± 0.26	
>25.75	0.96 ± 0.19		3.38 ± 0.32	

Table E5: Quality of life according to the interquartile time between diagnosis and study

	≤ 12.44	[12.44 - 19.45]	[19.45 - 25.75]	>25.75	p value
Physical functioning	85.15 ± 3.37	86.36 ± 2.84	89.98 ± 2.10	87.34 ± 2.51	0.686
Social functioning	76.68 ± 3.31	71.15 ± 3.34	71.25 ± 0.04	69.36 ± 3.76	0.510
Role: physical	74.00 ± 5.76	71.33 ± 5.30	66.84 ± 5.94	61.11 ± 5.43	0.384
Role: emotional	63.67 ± 4.46	53.06 ± 4.75	60.88 ± 4.50	57.52 ± 4.46	0.392
Mental health	71.28 ± 2.31	67.76 ± 2.15	69.06 ± 2.51	64.53 ± 3.18	0.307
Vitality	52.99 ± 3.07	53.43 ± 2.67	53.48 ± 2.90	52.82 ± 2.98	0.998
Bodily pain	73.08 ± 3.69	76.56 ± 3.23	70.08 ± 3.90	68.59 ± 3.52	0.415
General health	48.91 ± 3.40	46.24 ± 3.30	44.79 ± 3.30	39.85 ± 2.87	0.247
Physical composite score	48.21 ± 1.45	49.07 ± 1.22	47.72 ± 1.22	46.66 ± 1.24	0.580.
Mental composite score	45.70 ± 1.23	42.39 ± 1.25	43.79 ± 1.42	42.63 ± 1.54	0.306