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Prognostic and Serial Assessment of Functional/Psychosocial Factors in Older Adults Receiving AML Induction Chemotherapy

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Abstract:
Older adults with acute myeloid leukemia (AML) have a poor prognosis and high heterogeneity in terms of fitness and disease-related parameters, yet standardized assessment integrating patient-related factors is limited. We investigated the prognostic value of baseline health-related quality of life (HRQoL) and performance parameters in older adults undergoing induction chemotherapy (IC). In this multicenter, prospective study 82 patients ≥60 years with newly diagnosed AML were assessed over one year. Assessment included HRQoL, performance status, psychological distress, resilience, comorbidities, and functional independence. Primary endpoint was overall survival (OS), secondary endpoints HRQoL and psychological distress. Median age was 68 years. 62% proceeded to allogeneic transplantation. Median OS was 22.1 months. In multivariate analysis, none of the patient-related factors were significantly associated with OS; role functioning showed a non-significant tendency (p=0.083). High-risk cytogenetics (p=0.0198), elevated creatinine (p=0.027), and tAML (p=0.015) were significantly associated with reduced OS. Most HRQoL domains worsened initially but improved by 12 months, whereas cognitive function and resilience remained impaired. In summary, disease-related variables, rather than functional or psychosocial parameters, predicted OS. No significant influence of depression or anxiety on OS was observed. Persistent deficits in cognition and resilience highlight important targets for supportive interventions. German Clinical trial ID: DRKS00003601

Conflict of interest: COI declared - see note

COI notes: Michael Lübbert received honoraria from AbbVie, Astex, Janssen-Cilag, Otsuka, Syros; Cheplapharm (study drug for a clinical trial), J&J / EORTC (research support to institution), all unrelated to this work. Ulrich Germing reports speaker honoraria from Novartis, Janssen, and Bristol Myers Squibb, and institutional research support from AbbVie, Bristol Myers Squibb, and Jazz Pharmaceuticals, unrelated to the submitted work. Fabio Efficace had a consultancy or advisory role for AbbVie, Incyte, Novartis, JAZZ Pharmaceuticals. Research funding (institution) from Daiichi Sankyo and Otsuka. All outside the submitted work. All other authors declare no competing financial interests.

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Non-author contributions and disclosures: No;

Agreement to Share Publication-Related Data and Data Sharing Statement: For original data, please contact sophie.mersiowsky@uniklinik-freiburg.de or michael.luebbert@uniklinik-freiburg.de Deidentified individual participant data that support the findings of this study are available from the corresponding author upon reasonable request and subject to institutional and ethical approval.

Clinical trial registration information (if any): This trial was registered at the German Clinical trial register. ID: DRKS00003601 https://drks.de/search/en

Prognostic and Serial Assessment of Functional/Psychosocial Factors in Older Adults Receiving AML Induction Chemotherapy

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Data sharing statement:

For original data, please contact sophie.mersiowsky@uniklinik-freiburg.de or michael.luebbert@uniklinik-freiburg.de

Deidentified individual participant data that support the findings of this study are available from the corresponding author upon reasonable request and subject to institutional and ethical approval.

Key points

- HRQoL declined after induction but mostly recovered by 12 months, except for persistent impairments in cognitive function and resilience.
- OS was driven by AML-related factors; baseline HRQoL, depression, anxiety, and resilience showed no association with survival.

Abstract

Older adults with acute myeloid leukemia (AML) have a poor prognosis and high heterogeneity in terms of fitness and disease-related parameters, yet standardized assessment integrating patient-related factors is limited. We investigated the prognostic value of baseline health-related quality of life (HRQoL) and performance parameters in older adults undergoing induction chemotherapy (IC). In this multicenter, prospective study 82 patients ≥60 years with newly diagnosed AML were assessed over one year. Assessment included HRQoL, performance status, psychological distress, resilience, comorbidities, and functional independence. Primary endpoint was overall survival (OS), secondary endpoints HRQoL and psychological distress. Median age was 68 years. 62% proceeded to allogeneic transplantation. Median OS was 22.1 months. In multivariate analysis, none of the patient-related factors were significantly associated with OS; role functioning showed a non-significant tendency (p=0.083). High-risk cytogenetics (p=0.0198), elevated creatinine (p=0.027), and tAML (p=0.015) were significantly associated with reduced OS. Most HRQoL domains worsened initially but improved by 12 months, whereas cognitive function and resilience remained impaired. In summary, disease-related variables, rather than functional or psychosocial parameters, predicted OS. No significant influence of depression or anxiety on OS was observed. Persistent deficits in cognition and resilience highlight important targets for supportive interventions. German Clinical trial ID: DRKS00003601

Introduction

Acute myeloid leukemia (AML) is a disease of older adults, with a median age of 68 years at the time of diagnosis[1]. With only limited therapeutic options, the outcome is rather poor even today due to biological heterogeneity and variability in physical and mental fitness[2]. Induction chemotherapy (IC), often followed by hematopoietic stem cell transplantation (HCT) in older, fit AML patients has been the only curative treatment option for decades[3,4]. Since early mortality is higher than in younger patients, identification of pretreatment factors to better

predict which patients benefit most from IC is warranted. Among the potential prognostic factors influencing treatment response and survival, patient-reported outcomes (PROs) such as HRQoL are gaining importance[5]. However, only a limited number of studies on older fit AML patients have systematically captured PROs [6].

In a previous study, we investigated the prognostic value of HRQoL in 195 older patients diagnosed with AML or myelodysplastic syndrome (MDS) either treated with best supportive care (BSC), hypomethylating agents (HMA) or IC/HCT[7]. A 3-parameter-score indicating impairments of activities of daily living (ADL), reduced Karnofsky Performance Status (KPS) and patient-reported fatigue (by the EORTC QLQ-C30) was shown to reliably separate in the group of patients receiving non-intensive treatment regarding overall survival. However, in intensively treated patients, its prognostic effect was much weaker.
Further investigation of patient-related prognostic factors by exploring a broader set of baseline variables in a more homogeneous cohort of fit elderly patients is warranted.
We therefore investigated the prognostic value of HRQoL and performance parameters for overall survival (OS) in fit AML patients ≥ 60 years receiving IC, and assessed longitudinal changes in HRQoL and psychosocial parameters over 12 months.

Methods

Study design and patients

This was a prospective cohort observational study consecutively enrolling, between 2012 and 2020, patients ≥ 60 years with newly diagnosed AML scheduled to receive standard IC at three German centers. Therapy-related (tAML) and secondary (sAML) patients, and previous MDS therapy with HMAs were allowed. The primary endpoint was OS, secondary endpoints included HRQoL and psychological distress.

Patient-reported outcome assessment

A comprehensive geriatric and psychosocial assessment was performed at registration and at at 3, 6 and 12 months (+/- 4 weeks). The respective questionnaires were completed by the patients (paper version). HRQoL was measured using the EORTC (European Organization for Research and Treatment of Cancer) Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) version 3.0 (≥10-point changes considered clinically meaningful)[8]. Resilience was assessed with the German short form RS-11 (11-77 scoring, <60 indicative of reduced resilience)[9]. Depression and anxiety symptoms were assessed by the Hospital Anxiety and Depression Scale (HADS)[10].

Clinician-assessed and other non-patient-reported variables

Assessment at registration included Karnofsky Performance Status (KPS)[11], performance in daily self-care tasks by the ADL/Barthel Index[12], comorbidities (HCT-CI)[13] and the G8 geriatric screening tool[14]. We documented demographics, AML parameters (bone marrow and peripheral blood blasts, cytogenetics), vital signs, laboratory data (blood counts, serum lactate dehydrogenase (LDH), creatinine, albumin, fibrinogen) and ELN (European LeukemiaNet) 2010 AML risk classification[15].

KPS and ADL, blood counts and bone marrow cytology were re-assessed at 3, 6 and 12 months. The follow-up period for survival status and AML remission status was continued until one year after registration of the last patient (including contact by phone every 6 months).

Statistical analysis

Statistical analyses were performed with SAS 9.4 (SAS Institute Inc., Cary, NC, USA). OS was calculated as time from trial registration until death from any cause. Patients where the event of interest for OS was not observed were censored at the time of last follow-up.

OS was analyzed using the Kaplan Meier method and Cox proportional hazards regression models. Potential prognostic factors were preselected if a univariate $p<0.1$ was observed, followed by a multivariate model with a backward variable selection (stay in model if $p<0.1$). Factors were dichotomized based on known cutoff values, distributional aspects or interpretability considerations otherwise. HCT was additionally explored as a time-dependent covariate in survival analyses. Results are presented as hazard ratios (HRs) with two-sided 95% confidence intervals (CI). Longitudinal changes are analyzed descriptively based on observed values. No replacement of missing values was performed, as they mainly result from patients who died before the assessment. Results are displayed graphically with 95% CIs for means (calculated using t distribution).

Approval for the study of the Ethics Committee of the University of Freiburg from 27.03.2012 and renewed at 08.09.2019 for patient information and consent form (reference number 190716)

Results

Patient characteristics

82 patients ≥60 years (median age 68 years [IQR 64-72], 54% female) with newly diagnosed AML were enrolled. Median KPS was 80% [IQR 70-90]. The most common subgroup was de novo AML (82.9%), 10% had a tAML (Table 1). The most common IC was the 7+3 (cytarabine+daunorubicin) regimen (42.7%). 62.2% proceeded to allogeneic HCT. Median follow-up of all patients was 17.4 months, median OS was 22.1 months with a 30-day-mortality rate of 7.3% (n=6).

Prognostic value of baseline PRO and disease-related parameters

In univariate analyses, significant associations ($p < 0.05$) with OS were observed for several factors including: KPS <80% (HR 1.76, 95% CI 1.00-3.09, p=0.05), role functioning <50 (HR 2.35, 95% CI 1.32-4.19, p=0.004), physical functioning <50 (HR 1.91, 95% CI 1.06-3.46, p=0.031), and global HRQoL <50 (HR 1.85, 95% CI 1.04-3.29, p=0.038). Additionally, disease-related factors including high-risk cytogenetics (HR 2.47, 95% CI 1.28-4.76, p=0.007), creatinine >1.1 mg/dL (HR 2.15, 95% CI 1.19-3.86, p=0.011), and tAML (HR 2.52, 95% CI 1.21-5.29, p=0.014) showed significant associations.

In the final multivariate analysis obtained after backward selection, no patient-related factor remained statistically significant, with role functioning <50 showing a trend towards significance (HR 1.76, 95% CI 0.93-3.31, p=0.083). Disease-related factors like high-risk cytogenetics (HR 2.25, 95% CI 1.14-4.45, p=0.020), elevated creatinine (HR 2.11, 95% CI 1.09-4.08, p=0.027) and tAML (HR 2.62, 95% CI 1.21-5.68, p=0.015) remained independently associated with OS (Table 2). Inclusion of HCT as a time-dependent covariate did not substantially change the results

Analysis of HRQoL changes over time by the EORTC QLQ-C30

Overall, 34 of 82 patients (41.4%) completed all scheduled patient-reported outcome assessments, including baseline and the 3-, 6-, and 12-month follow-up evaluations (EORTC QLQ-C30, HADS-A/D, and RS-11). Compliance with the EORTC QLQ-C30 questionnaire was 97.5% at baseline (80/82 patients) and 83.0% (58/70 patients alive), 90.5% (57/63 patients alive), and 82.7% (43/52 patients alive) at 3, 6, and 12 months, respectively.

Functional aspects and Global HRQoL

At 3 months, physical (-12 points), social (-14 points), and role functioning (-17.5 points) showed clinically meaningful deteriorations, which gradually improved and approached or surpassed baseline values by 12 months. Emotional functioning improved from the outset and

was sustained over time. In contrast, cognitive functioning showed an early and persistent deterioration (–7 to –8 points at follow-ups). Global HRQoL constantly increased over time, thus reaching a clinically relevant improvement at 12 months (+12 points, Figure 1).

Symptoms

Fatigue (+5 points), appetite loss (+15 points) and nausea/vomiting (+9 points) showed deterioration at 3 months but improved during follow-up, ultimately scoring better than at baseline. Dyspnea (–6 points) and insomnia (–7 points) showed sustained improvement already at 3 months, with further decreases at 12 months. Constipation and diarrhea showed no clinically relevant changes (Figure 1).

Psychosocial Parameters

Anxiety and depression remained largely stable, with 27-35% of the patients showing mild symptoms during follow-up and ≤5% with severe symptoms. Mean HADS-A/-D scores stayed below clinical threshold. In contrast, resilience declined over time (baseline mean of 65.4 declining to 59-62 points during follow-up, and reduced resilience in 27.5% at baseline versus 45-51% at follow-up time points, Figure 3).

Discussion

To date, decision-making for or against IC in older AML patients mainly involves toxicity studies, comorbidities, and disease characteristics, while PROs - particularly psychosocial measures - are rarely represented, despite early evidence showing influence on both treatment decisions and HRQoL outcomes[16]. We conducted a study to evaluate a similar geriatric assessment as previously performed by Deschler et al. (2013) in a homogeneous cohort including AML patients ≥60 years fit for IC at diagnosis. Patients were prospectively assessed at three follow-up time points over 12 months, including HRQoL (EORTC QLQ-C30), HADS, and resilience (RS-11) to examine both prognostic values and longitudinal trajectories[17,18].

In multivariate analysis, none of the patient-related factors were significantly associated with OS, although role functioning showed a non-significant trend. Role functioning refers to a patient's ability to fulfill their usual responsibilities in daily life, including work, family, and social roles. This item captures the complex impact of restrictions in this field on the individual health status of AML patients undergoing intensive treatment.

As high-risk cytogenetics, tAML and elevated creatinine were significantly associated with shorter OS, the relevance of disease-related factors is again demonstrated in this study and underlines the importance of a comprehensive analysis of these characteristics[19,20].

However, detailed assessments like the EORTC QLQ-C30 provide valuable insights, but complex assessments may not always be indicated in all clinical scenarios[21]. The decision to employ such assessments should be guided by the specific clinical context.

Prospective HRQoL assessment demonstrated an early decline for several functional and symptom aspects scales at 3 months, particularly physical and role functioning, and appetite loss and fatigue, likely reflecting the acute toxicities and treatment burden of IC. Most domains subsequently improved with recovery toward baseline levels by 12 months. This data is corroborated by previous evidence in younger and older patients, albeit using other questionnaires[17,22]. Longer-term PRO trajectories, however, cannot be attributed solely to IC, as subsequent treatments, relapse status, comorbidities and changes in psychosocial circumstances may also have influenced the recovery patterns,

We observed a persistent impairment of cognitive functioning, which is broadly in keeping with the findings of Efficace et al. (2024), where a decline in cognitive function up to 12 months was shown in both groups (HMA and 7+3 cohort)[23]. We additionally observed a persistent decline in resilience. Patients may adapt to some physical limitations over time, but the impact on their cognitive function and overall resilience may be more lasting and indicates a need for specific supportive measures during the course of treatment, and also during long-term follow-up.

Symptoms of anxiety and depression were generally mild, stable over time, with no significant increase in risk. In older AML patients, the relationship between psychological distress and survival appears complex: the presence of depression and anxiety symptoms alone seems not to have a direct independent association with OS but may affect HRQoL and treatment adherence[17]. Therefore, addressing psychological distress remains a crucial component of comprehensive patient care.

This study has several limitations, including the sample size, the risk stratification based on ELN 2010 criteria (standard at study initiation and therefore lacking additional molecular markers) and the relatively high proportion of patients with favorable/intermediate-risk AML, which may have contributed to more favorable PRO recovery trajectories.

Recent developments in treatment strategies for AML are increasingly highlighting the importance of HMA/venetoclax-based therapy. Although these lower-intensity approaches were originally established for unfit, older patients, recent prospective data such as from the PARADIGM study suggest efficacy in terms of disease control with improved QoL for young, fit patients as well[24,25]. Treatment intensity alone may no longer define optimal care, underscoring the need to reconsider how biological and patient-related factors are both integrated into clinical decision-making. For now, IC selection in older AML patients remains primarily guided by disease-related characteristics, as also confirmed by recent data from the Beat AML Master Trial[26]. Nonetheless, systematic evaluation of HRQoL, cognitive function, and resilience can improve supportive care strategies and optimize recovery during and after treatment.

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Authorship Contributions: M.L. conceived and designed the study. B. D.-B. contributed to study conception, protocol development and funding acquisition. U.G., B.H. and V.A. were responsible for patient recruitment and data acquisition at participating centers. G.I. performed the statistical analysis. S.-L. M., V.A., G.I. and M.L. interpreted the data. S.-L. M., G.I., F.E. and M.L. wrote the manuscript. All authors critically revised the manuscript, and approved the final version

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Tables

Table 1. Patient characteristics.

Characteristic n = 82	Number (%)
Sex	
male	38 (46.3)
female	44 (53.7)
Age – years	
median	68 [64-72]
range	60 – 81
PB blasts – %	
median	35 [6-73]
range	0 – 97
WBC – 1000/µl	
median	22.4 [2.61-46.41]
range	0.65 – 269
Hb – g/dl	
median	8.05 [7.4-9.7]
range	5.9 – 15.0
PLT – 1000/µl	
median	46.0 [29-94]
range	4.0 – 248
Karnofsky Performance Status (KPS)	
median	80 [70-90]
range	40 - 100
ELN 2010 risk stratification	
favorable	24 (29.3)
intermediate I	26 (31.7)
intermediate II	14 (17.1)
adverse	15 (18.3)
no data available	3 (3.6)
AML	
De novo AML	68 (82.9)
sAML	6 (7.3)
tAML	8 (9.8)
Induction therapy	
7+3	35 (42.7)
MICE	27 (32.9)
other	20 (24.4)
HCT	
HCT	51 (62.2)
No HCT	31 (37.8)

Abbreviations: PB: peripheral blood; WBC: white blood cell count; Hb: hemoglobin; PLT: platelet count; ELN: European Leukemia Network; sAML: secondary AML; tAML: treatment-related AML; 7+3: chemotherapy regimen consisting of 7 days cytarabine + 3 days daunorubicin; MICE: mitoxantrone, ifosfamide, carboplatin, etoposide; HCT: hematopoietic stem cell transplantation. Values are reported as median [IQR, 25th–75th percentile].

Table 2. Univariate and multivariate Cox proportional hazards models of baseline factors associated with OS.

	Univariate analysis		Multivariate analysis	
Parameter	Hazard Ratio (95% CI)	P value	Hazard Ratio (95% CI)	P value
Patient related factors				
KPS < 80%	1.76 (1.00, 3.09)	0.0499	-	-
HADS-D ≥ 8	1.06 (0.99, 1.13)	0.0830	-	-
HCT-CI ≥ 3	1.62 (0.88, 3.00)	0.1213	-	-
Age ≥ 65	1.50 (0.79, 2.83)	0.2141	-	-
Resilience scale (RS11) ≥ 70	1.45 (0.80, 2.61)	0.2220	-	-
ADL < 100	1.31 (0.70, 2.45)	0.3913	-	-
G8 frailty < 14	1.25 (0.70, 2.24)	0.4585	-	-
HADS-A ≥ 8	0.95 (0.53, 1.70)	0.8714	-	-
EORTC QLQ-C30 domains				
Financial difficulties ≥ 50	3.51 (1.56, 7.87)	0.0024	-	-
Role functioning < 50	2.35 (1.32, 4.19)	0.0036	1.76 (0.93, 3.31)	0.0825
Constipation ≥ 50	2.59 (1.16, 5.80)	0.0209	2.33 (1.00, 5.38)	0.0489*
Physical functioning < 50	1.91 (1.06, 3.46)	0.0314	-	-
Dyspnea ≥ 0	1.87 (1.05, 3.30)	0.0323	-	-
Global HRQOL< 50	1.85 (1.04, 3.29)	0.0377	-	-
Fatigue ≥ 50	1.59 (0.88, 2.87)	0.1279	-	-
Diarrhea ≥ 50	0.84 (0.39, 1.80)	0.6555	-	-
Disease-related factors				
High risk cytogenetics	2.47 (1.28, 4.76)	0.0070	2.25 (1.14, 4.45)	**0.0198**
Creatinine > 1.1 mg/dl	2.15 (1.19, 3.86)	0.0108	2.11 (1.09, 4.08)	**0.0265**
Treatment-related AML	2.52 (1.21, 5.29)	0.0140	2.62 (1.21, 5.68)	**0.0145**
WBC > $3x10^9$/L	1.63 (0.83, 3.18)	0.1556	-	-
HCT received (time-dependent)	1.33 (0.70, 2.52)	0.3800	-	-

OS of older AML patients receiving induction therapy is strongly dependent on disease-related factors like high risk cytogenetics, creatinine and treatment-related AML, all of which remained independently associated with worse outcomes in multivariate analysis. Regarding the psychosocial context, among patient-reported outcomes, none of them were significantly associated with OS, only *role functioning* shows a non-significant trend. *Constipation is not considered to be relevant due to small patient numbers. Only variables retained after backward selection are shown.

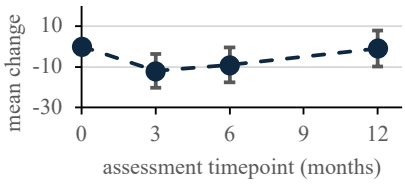
Abbreviations: HADS-A/D: hospital anxiety and depression scale-anxiety/depression, HCT-CI: Hematopoietic Cell Transplantation-specific Comorbidity Index, ADL: activities of daily living, G8: G8 geriatric screening tool, WBC: white blood cell count, OS: overall survival.

Figure legend:

Figure 1. Baseline (BL) score, mean change from baseline to 3, 6 and 12 months and 95% confidence intervals on selected scales from the EORTC QLQ-C30, HADS-A/D and RS-11. Functioning scale: higher scores indicate better functioning. Symptoms, anxiety, depression: higher scores indicate higher severity. Resilience: higher scores indicate higher resilience. Global HRQoL: higher scores indicate better QoL.

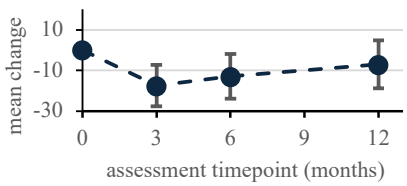
Figure 1

physical functioning



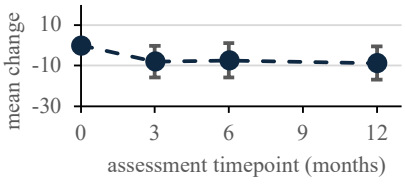
HRQoL assessment	Mean change (95% CI)	n
BL score	64.7 (58.6, 70.7)	80
3 months	-12.0 (-20.3,-3.8)	57
6 months	-9.0 (-17.7, -0.3)	57
12 months	-0.9 (-9.9, 8.0)	43

role functioning



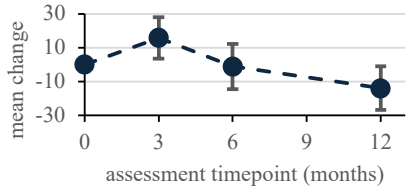
HRQoL assessment	Mean change (95% CI)	n
BL score	54.0 (46.4,61.5)	80
3 months	-17.5 (-27.7, -7.4)	57
6 months	-12.9 (-24.0, -1.8)	57
12 months	-7.0 (-18.7, 4.7)	43

cognitive functioning



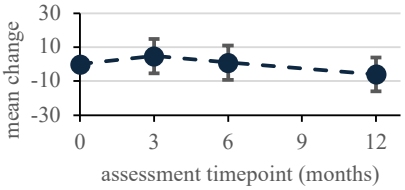
HRQoL assessment	Mean change (95% CI)	n
BL score	77.2 (71.3, 83.2)	79
3 months	-8.0 (-15.9, -0.2)	56
6 months	-7.4 (-15.9, 1.1)	56
12 months	-8.7 (-17.1, -0.4)	42

appetite loss



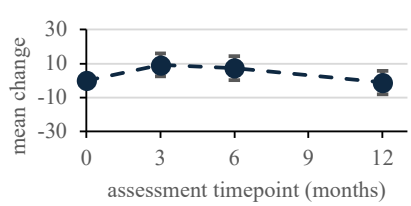
HRQoL assessment	Mean change (95% CI)	n
BL score	39.6 (31.1, 48.0)	80
3 months	15.8 (3.6, 28.0)	57
6 months	-1.2 (-14.7, 12.4)	57
12 months	-14.0 (-26.9, -1.0)	43

fatigue



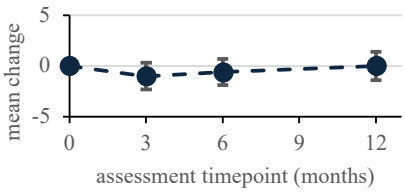
HRQoL assessment	Mean change (95% CI)	n
BL score	57.6 (50.7,64.6)	80
3 months	4.9 (-5.3, 15.0)	57
6 months	1.0 (-9.2, 11.1)	57
12 months	-5.9 (-15.9, 4.0)	43

nausea and vomiting



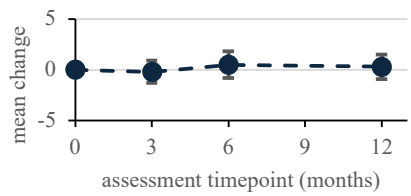
HRQoL assessment	Mean change (95% CI)	n
BL score	9.6 (5.5, 13.7)	80
3 months	9.1 (2.3, 15.9)	57
6 months	7.3 (0.2, 14.4)	57
12 months	-1.2 (-8.2, 5.9)	43

anxiety



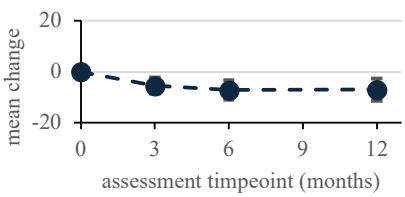
HRQoL assessment	Mean change (95% CI)	n
BL score	6.7 (5.7, 7.8)	80
3 months	-1.0 (-2.3, 0.3)	57
6 months	-0.6 (-1.9, 0.7)	57
12 months	0.0 (-1.3, 1.4)	43

depression



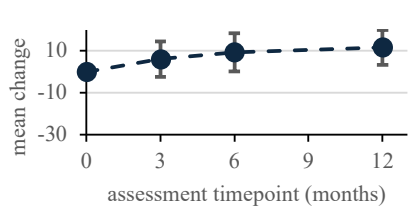
HRQoL assessment	Mean change (95% CI)	n
BL score	5.8 (4.8, 6.7)	80
3 months	-0.2 (-1.3, 0.9)	57
6 months	0.5 (-0.8, 1.8)	57
12 months	0.3 (-0.9, 1.5)	43

resilience



HRQoL assessment	Mean change (95% CI)	n
BL score	65.4 (63.2, 67.5)	80
3 months	-5.5 (-8.7, -2.3)	52
6 months	-7.2 (-11.1,-3.2)	53
12 months	-7.0 (-11.4, -2.7)	41

global HRQoL



HRQoL assessment	Mean change (95% CI)	n
BL score	45.8 (40.3, 51.3)	79
3 months	6.1 (-2.3, 14.5)	56
6 months	9.4 (0.2, 18.5)	56
12 months	11.7 (3.3, 20.1)	42