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Quality of life, neurocognitive functioning, psychological issues, sexuality and comorbidity more than 2 years after commencing immune checkpoint inhibitor treatment

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ABSTRACT

Background Increasing numbers of patients diagnosed with advanced cancer survive long-term after treatment with immune checkpoint inhibitors (ICIs). To design adequate interventions for these survivors, knowledge regarding quality of life (QOL) and its association with long-term and late effects of ICI treatment is required. Therefore, this study aimed to evaluate QOL, neurocognitive function, psychological issues, sexuality, and comorbidities in patients surviving at least 2 years after commencing ICI treatment.

Methods We performed a cross-sectional study in patients with stage III-IV melanoma, non-small cell lung cancer (NSCLC), urothelial cell carcinoma (UCC), or renal cell carcinoma (RCC) who survived at least 2 years after the start of ICIs. We assessed QOL, neurocognitive function, psychological issues, sexual function and comorbidity in survivors. Additionally, we evaluated QOL of informal caregivers.

Results 132 survivors (70 melanoma, 50 NSCLC, 12 UCC or RCC) and 80 caregivers were included. Median age was 65 years (range 30–85) and 50 survivors were women (38%). Median time since start and cessation of ICI treatment was 33 (range 21–91) and 18 (range 0–68) months, respectively. Average survivor QOL was comparable to the reference population, but 37 (28%) survivors had poor QOL. Depression and anxiety were negatively correlated with all QOL domains. Although immune-related adverse events were common, there was no association with lower QOL. Caregiver and survivor QOL were only weakly related. Neurocognitive concerns and formally tested neurocognitive impairment were present in 22 (17%) and 13 (15%) survivors, respectively, and were not associated with a diagnosis of brain metastases. Men had a high prevalence of erectile dysfunction and low sexual satisfaction. Half of the survivors met the criteria for the metabolic syndrome.

Conclusions At least 2 years after the start of ICI treatment, one-quarter of cancer survivors had a clinically relevant lower QOL. This was associated with symptoms of depression and anxiety, but not with immune-related adverse events. Sexual issues and metabolic syndrome are prevalent. Survivorship care should address these issues in this population.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Long-term survivors of immune checkpoint inhibitor (ICI) treatment generally maintain their quality of life (QOL), but specific challenges such as depression and anxiety are prevalent.

WHAT THIS STUDY ADDS

⇒ This study identifies that approximately one-quarter of ICI survivors experience poor QOL, with significant issues related to mental health, sexual function, and metabolic syndrome.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The findings highlight the need for targeted interventions to address these issues and suggest that caregiver support should be integrated into survivorship care plans.

BACKGROUND

The introduction of immune checkpoint inhibitors (ICIs) ushered in a new treatment era for many types of advanced cancer, including melanoma, non-small cell lung cancer (NSCLC), urothelial cell carcinoma (UCC), and renal cell carcinoma (RCC). While survival in these patient groups was limited in the past, ICI treatment changed this scenario. For example, in metastatic melanoma, the median overall survival increased from less than 12 months to almost 72 months.[1] Furthermore, responses to ICIs are often durable, with survival curves plateauing after 2–3 years. These advances have resulted

in a new and growing population of long-term survivors of advanced cancer (referred to as advanced cancer survivors). Moreover, ICIs have moved to adjuvant and neoadjuvant settings, further expanding the group of patients exposed to this type of agent.[2 3]

Cancer survivors may suffer from both long-term treatment-related sequelae and the psychosocial impact of being diagnosed with a life-threatening disease. ICIs induce an anticancer immune response that can result in serious immune-related adverse events (irAEs), most commonly affecting the skin, endocrine organs, gastrointestinal tract, lungs, and liver. Most irAEs are reversible after ICI interruption and (prolonged) treatment with corticosteroids or other immunosuppressants.[4] However, consequences of endocrine irAEs, for example, hypothyroidism after thyroiditis, and loss of function of the thyroid and adrenal axis due to hypophysitis are usually long-lasting and require life-long hormonal substitution. A meta-analysis reported increased treatment benefit in patients experiencing irAEs compared with patients without these AEs.[5] This relationship was observed in various cancer types. This suggests that the prevalence of irAEs, including their long-term sequelae, may be higher in long-term survivors.

In addition, cancer survivors may suffer from psychological issues (anxiety, depression, fear of recurrence, and existential distress), neurocognitive dysfunction, and work-related issues.[6 7] However, most previous studies in cancer survivors were performed in patients who were treated with curative intent prior to the implementation of ICIs. The large ICI registration trials did include quality of life (QOL) assessments, but the follow-up length and reporting of outcomes vary widely across studies. It is well known that trial populations often do not represent the real-world population. A Danish study demonstrated that of the 276 patients with metastatic melanoma who were referred to the medical oncologist in 2014, 152 (55%) did not meet one or more inclusion criteria of the phase III ICI registration study. Despite this, 114 of these 152 patients did receive ICI treatment.[8] This limits the generalizability of the QOL outcomes of registration trials.

Previous studies in patients achieving long-term survival after ICI treatment showed variable QOL outcomes, while RCTs (randomized controlled trials) showed no worsening of QOL.[9–18] Furthermore, an increased prevalence of depression and post-traumatic stress disorders has been reported.[9–11 17 19] Unfortunately, most of these studies had small samples (<100 survivors) and lacked caregiver QOL assessments. Only three small studies (n≤25) evaluated neurocognitive functioning.[9 10 20]

We assessed QOL, neurocognitive functioning, psychosocial issues, and somatic health outcomes in a large cohort of patients with melanoma, NSCLC, UCC, and RCC surviving at least 2 years after the start of ICI treatment. Additionally, the QOL of their informal caregivers was evaluated.

METHODS

Study design and population

This cross-sectional study included patients who survived at least 2 years after the start of ICIs at the Comprehensive Cancer Center of the University Medical Center Groningen (UMCG), the Netherlands. For each patient, one informal caregiver was also invited to participate. Inclusion criteria for patients were: age ≥18 years; diagnosis of melanoma, NSCLC, UCC, or RCC; at least 2 years after the start of ICI; and no treatment changes due to disease activity for at least 2 months prior to study inclusion. We excluded patients who had previously been treated for other malignancies (excluding non-melanoma skin cancer, cervical intraepithelial neoplasia, or carcinoma in situ of the breast); patients unable to understand or abide by the study protocol; and those suffering from debilitating psychiatric illnesses. Patients were allowed to have received other antitumor treatments prior to, during, or after the ICI treatment. Patients were included between October 2018 and June 2022.

Study procedures

Study measurements were performed during a single study visit. Demographics, smoking status, and work information before and after treatment with ICIs were obtained through structured interviews. Retrospective chart review was performed to extract disease variables (time of diagnosis, presence of brain metastases, disease stage at time of start ICIs and at time of study visit), treatment variables, and irAEs of any grade CTCAE—Common Terminology Criteria for Adverse Events V.5.0 (type, onset, severity, duration of irAE, and received treatments for irAE). All irAEs between the start of ICI and the study visit were included. Ongoing toxicity was defined as: still receiving active treatment for or due to the irAEs (eg, prednisolone or other hormonal substitution) at the time of the study visit. Caregivers completed a single self-report questionnaire at home around the same time as the patient's study visit. Research Electronic Data Capture System (REDCap), a secure web application, was used to build and manage the study database.[21] Below, study procedures are described in detail.

Physical examination

Weight, height, waist, and hip circumference were measured. Blood pressure was recorded after 10 min of rest in a supine position using an automatic device.

Self-report questionnaires

- European Organization for the Research and Treatment of Cancer Quality-of-Life Questionnaire (EORTC QLQ-C30)[22] measures the QOL of patients with cancer. The 30-item questionnaire contains a global health scale and several functional and symptom subscales. The global health scale and the five functional scales (physical, role, emotional, cognitive, and social) were used in the current study. All scores were transformed to a 0–100 scale, with higher

scores indicating better QOL. Scores were compared with the normative data for the EORTC QLQ-C30 in the general Dutch population (n=1,000).[23] Differences of more than 10 points on a subscale were considered clinically significant.[23]

Hospital Anxiety and Depression Scale (HADS)[24] measures the presence of depressive and anxiety symptoms in the past week. It consists of two 7-item subscales on depressive symptoms and anxiety symptoms, and all items are scored on a 4-point Likert scale. Subscale scores of ≥8 indicate at least mild anxiety or depressive symptoms.

- Functional Assessment of Cancer Therapy-Cognitive Function V.3 (FACT-Cog)[25] was added in December 2019 to examine the presence and severity of neurocognitive concerns. The questionnaire includes 37 items related to perceived neurocognitive impairment and functioning, impact on QOL, and received comments from others on neurocognitive functioning. The perceived neurocognitive impairment subscale (FACT-Cog PCI - Perceived Cognitive Impairment) was used in the current study. The FACT-Cog PCI includes 18 items, scored on a 5-point scale (subscore range from 0 to 72), with higher scores indicating less neurocognitive concerns. A score of 54 was used as the cut-off.[26]
- The Global Measure of Sexual Satisfaction (GMSEX)[27] was used to assess sexual satisfaction. It consists of five items on a 7-point Likert scale: good-bad, pleasant-unpleasant, positive-negative, satisfying-unsatisfying, and valuable-worthless. Ratings are summed with a total score ranging from 5 to 35, with higher scores indicating greater sexual satisfaction. Men were asked to fill out the International Index of Erectile Function (IIEF),[28] which comprises 15 questions on a 5 or 6-point Likert scale and assess five domains: erectile function, orgasmic function, sexual desire, intercourse satisfaction and overall satisfaction. We focused on the erectile function subscale, where the score may range from 1 to 30. A score <14 is used to determine if additional investigation is indicated.[28]
- Caregiver Quality of Life Index-Cancer (CQOLC)[29] consists of 35 items that assess the QOL of caregivers of patients with cancer. The CQOLC produces a total score and four subscores: caregiver burden, disruptiveness, positive adaptation, and financial concerns. Items are scored on a 5-point Likert scale, resulting in a final score between 0 and 140, with higher scores indicating better QOL. One informal caregiver per survivor was asked to fill out this questionnaire.

Neuropsychological tests

The International Cancer and Cognition Task Force[30] recommended neuropsychological tests be performed with the addition of the Digit Span Test to further examine working memory.

- Hopkins Verbal Learning Test-Revised (HVLT-R)[31] includes a measure of verbal learning (HVLT-R total recall) and a measure of memory (HVLT-R delayed recall).
- Trail Making Test[32] (TMT) assesses processing speed and visual attention (TMTA) and executive functioning and mental flexibility (TMTB).
- Controlled Oral Word Association (COWA)[33] evaluates verbal fluency.
- Digit Span Test[34], a subtest of the WAIS-R battery (Wechsler Intelligence Test-Revised), measures auditory attention and working memory. The total test score of the subtests forward, backward, and ordering digit range was used in the current study.

Based on normative norms, the test scores were converted into *z*-scores accounting for gender, age, and/or education.[31 35] Neurocognitive impairment was defined as two or more scores 1.5 SD below the normative mean or a single test score ≥2 SD below the mean. According to the Ingraham and Aiken methodology (i.e., considering the probability of exceeding the cut-off scores for neurocognitive impairment while using six neuropsychological test scores), the chances of scoring 2 or more tests 1.5 SD and scoring a single test ≥2 SD below the mean in any random population are 14.1% and 5.6%, respectively.

Measurements in blood

Fasting blood samples were drawn, preferably between 08:00 and 10:00, to measure lipid profile, hormones, glucose, Hemoglobin A1c (HbA1c), and creatinine. Lipid profile included total cholesterol, triglycerides, high-density lipoprotein-cholesterol (HDL-C), and low-density lipoprotein-cholesterol. Hormone measurements included thyroid-stimulating hormone (TSH), free thyroxine, luteinizing hormone (LH), total testosterone, prolactin, cortisol, adrenocorticotropic hormone, and sex hormone-binding globulin. Albumin was measured to calculate free testosterone. All measurements in blood were performed by the hospital laboratory according to standard protocols.

6-minute walk test

Participants walked as far as possible in a 30 m course following international guidelines.[36] The total distance walked in 6 min was recorded as a measure of physical condition. The results were compared with the predicted distance based on data from healthy individuals, corrected by age, height and weight. We used the standard lower limit of normal to identify participants with poor physical condition.[37]

Metabolic syndrome

Metabolic syndrome was defined according to the unified International Diabetes Federation, American Heart Association and the National Heart, Lung, and Blood Institute criteria,[38] with the exception of hypertension where we considered that one blood pressure measurement at the study visit was not enough to classify a patient as having hypertension, conform hypertension definition of the European Society of Cardiology.[39] For the diagnosis of

metabolic syndrome, patients needed to have at least three out of the following five cardio-metabolic abnormalities:

- Elevated waist circumference: ≥102 cm in men and ≥88 cm in women.
- Elevated triglycerides: drug treatment for elevated triglycerides or triglyceride levels of ≥150 mg/dL (1.7 mmol/L).
- Reduced HDL-C: drug treatment for reduced HDL-C or HDL-C levels of <40 mg/dL (1.0 mmol/L) in men and <50 mg/dL (1.3 mmol/L) in women.
- Elevated blood pressure: antihypertensive drug treatment in a patient with a history of hypertension.
- Elevated fasting glucose: glucose-lowering agents or elevated fasting glucose of ≥100 mg/dL (5.6 mmol/L).

Statistical analyses

Statistical analyses were performed using SPSS V.29.0 (IBM SPSS Statistics, Armonk, New York, USA). Descriptive statistics were reported using mean and SD or median and range, depending on data distribution. Frequencies and percentages were used for categorical variables. Data distribution was determined using Kolmogorov-Smirnov tests, histograms, and Q-Q plots. The EORTC QLQ-C30 subscale means were compared with normative data using unilateral one-sample t-test. T-test and Mann-Whitney U test were used to test differences for normally distributed or skewed data, respectively. Correlations were tested using Pearson or Spearman, depending on data linearity.

The determinants of the different aspects of QOL (global health status, physical, role, emotional, cognitive, and social functioning) were identified through univariate and subsequent backward multivariate linear regression analyses. In online supplemental table 1a, the factors entered in the univariate analyses per different functional subscales of the EORTC QLQ-C30 are shown. Subsequently, all factors univariately associated with QOL measures with a p value of ≤0.05 were included in the multivariate regression analyses. Assumptions for linear regression analyses, for example, linear relationships and normally distributed residuals, were tested.

RESULTS

General characteristics

In total, 213 patients were approached for the study, and 144 provided informed consent (68%, online supplemental figure 1). Nine patients withdrew their consent, and three patients deteriorated due to disease progression and were no longer eligible. Eventually, 132 patients completed the study visit (table 1). Median age at the time of study was 65 years (range 30–85). 77 patients (58%) were working prior to the start of ICIs and 41 (31%) at the time of study. Of the 37 patients (28%) who stopped working, 10 (8%) patients retired (early) and 27 (21%) reported the inability to work due to physical or mental problems. The latter group had lower global health scores and significantly more depression issues, compared with survivors working at the study visit.

Treatment-related outcomes

Table 1 and figure 1 show treatment details. 70 patients (53%) had ongoing complete disease response. Median time since start and cessation of ICI treatment and study visit was 33 months (range: 21–91) and 18 months (range: 0–68), respectively. Table 2 shows the prevalence of irAEs, and online supplemental table 2 details the types and frequencies. Endocrine toxicity was the most common irAE, especially thyroiditis (n=34) and hypophysitis (n=15). All 48 patients with grade 2 endocrine AE experienced ongoing toxicity. Cutaneous (n=33, 20%) and rheumatic (n=23, 14%) toxicities were common grade 2 irAEs, but often not present anymore during the study visit. Gastrointestinal toxicity was the most common grade 3/4 irAE. ICI treatment was stopped in 31 patients due to an AE.

Quality of life

The mean EORTC QLQ-C30 scores of global health status and emotional functioning were not significantly different from the reference general Dutch population.[23] Cancer survivors scored lower on the subscales physical, role, cognitive and social functioning, although the differences were of small clinical relevance (<10 points, table 3). The subscore distribution is listed in online supplemental table 1b. 37 survivors (28%) reported a clinically relevant lower global health status, and 16 (43%) of them had at least mild depression or anxiety. Global health status was univariately associated (p≤0.05) with cancer type (driven by the difference between melanoma and NSCLC), being in a relationship, the severity of depressive/anxiety symptoms, reported neurocognitive concerns, 6-minute walk test (6MWT) and GMSEX-score (online supplemental table 1a). In the multivariate model, only a negative association with the severity of depressive/anxiety symptoms (β=−1.90, p<0.001) remained. The multivariate model explained 45% of the variance in global health status.

For the physical functioning scale, only the severity of depressive/anxiety symptoms, 6MWT performance and GMSEX score remained significant in the multivariate analysis. For cognitive and social functioning, negative associations with the severity of depressive/anxiety symptoms and reporting neurocognitive concerns remained significant in the multivariate model. For both the role and emotional functioning, only the severity of depressive/anxiety symptoms was significantly associated. Online supplemental table 1a includes the univariate and multivariate regression analyses outcomes per functioning scale.

Cognition

Table 3 shows cognitive concerns and impairment. Most affected neurocognitive domains (≥1.5 SD from the normative mean) were verbal learning, memory, auditory attention and working memory. Survivors who had received other systemic treatments besides ICIs did not score worse on neuropsychological tests than patients who had only received ICIs (18% vs 16%, p=0.75). The

Table 1 General and treatment characteristics

	Total	Melanoma	NSCLC	UCC/RCC
	(n=132)	(n=70)	(n=50)	(n=12)
Sex, (women)	50 (38%)	28 (40%)	19 (38%)	3 (25%)
Age at study visit (years)				
≤45	4 (3%)	3 (4%)	0 (0%)	1 (8%)
46–60	42 (32%)	27 (39%)	14 (28%)	2 (17%)
61–75	76 (57%)	35 (50%)	33 (66%)	7 (58%)
>75	10 (8%)	5 (7%)	3 (6%)	2 (17%)
Education*				
Low	27 (20%)	8 (12%)	16 (32%)	3 (25%)
Middle	53 (40%)	33 (47%)	17 (34%)	3 (25%)
High	52 (40%)	29 (41%)	17 (34%)	6 (50%)
In a relationship, (yes)	114 (86%)	63 (90%)	44 (88%)	12 (100%)
Have children, (yes)	107 (81%)	61 (87%)	36 (72%)	10 (83%)
AJCC TNM stage†				
Stage III	29 (22%)	12 (17%)	16 (32%)	1 (8%)
Stage IV	103 (78%)	58 (83%)	34 (78%)	11 (92%)
Brain metastases, (yes)	34 (26%)	24 (34%)	8 (16%)	2 (17%)
Treated with SRT/SRS	22 (17%)	12 (17%)	8 (16%)	2 (17%)
Treated with WBRT	1 (1%)	1 (1%)	0 (0%)	0 (0%)
Number of ICI lines				
1	113 (86%)	52 (74%)	49 (98%)	12 (100%)
2	17 (13%)	16 (23%)	1 (2%)	0 (0%)
3	2 (1%)	2 (3%)	0 (0%)	0 (0%)
Type of received ICI‡				
PD-1/PD-L1	114 (86%)	58 (83%)	46 (92%)	9 (75%)
CTLA-4	20 (15%)	19 (27%)	0 (0%)	0 (0%)
PD-1 plus CTLA-4	15 (11%)	9 (13%)	4 (8%)	3 (25%)
Median time since (months)				
Diagnosis of stage III-IV	44.0 (25–198)	44.0 (25–198)	41.5 (25–105)	65.0 (26–84)
Start ICI§	33.0 (21–91)	35.0 (21–91)	28.5 (21–65)	51.5 (24–73)
Stop ICI¶	18.0 (0–68)	20.0 (0–64)	15.0 (0–40)	30.5 (1–68)
Months of ICI treatment				
≤6	21 (16%)	17 (24%)	3 (6%)	1 (8%)
6–12	43 (33%)	25 (36%)	18 (36%)	3 (25%)
13–24	53 (40%)	22 (31%)	21 (42%)	7 (59%)
>24	15 (11%)	6 (9%)	8 (16%)	1 (8%)
Other systemic treatment‡				
Chemotherapy	63 (48%)	4 (6%)	39 (78%)	6 (50%)
Targeted therapy	44 (33%)	25 (36%)	3 (6%)	2 (17%)
Other	2 (1%)	1 (1%)	0 (0%)	1 (8%)
Adverse event—any**				
Grade 1–2	86 (65%)	43 (61%)	34 (68%)	9 (75%)
Grade 3/4	24 (18%)	13 (19%)	9 (18%)	2 (17%)
Ongoing toxicity	60 (46%)	27 (39%)	25 (52%)	8 (67%)

Continued

Table 1 Continued

	Total	Melanoma	NSCLC	UCC/RCC
	(n=132)	(n=70)	(n=50)	(n=12)

*Low: at maximum primary education and <2 years of low-level secondary education, middle: finished average-level secondary education, high: finished high-level secondary education or university degree.
†At time of start of immune checkpoint inhibitor treatment.
‡Patients could have received multiple systemic or localized treatments.
§Due to logistics, one patient had his/her study visit 6 weeks before the 2 years after start of treatment mark.
¶Five patients were still on ICI treatment at time of study visit.
**Number of patients with at least one adverse event related to ICI.
CTLA-4, Cytotoxic T-lymphocyte associated protein 4; ICI, immune checkpoint inhibitors; ICI, immune checkpoint inhibitor; NSCLC, non-small cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed cell death-ligand 1; RCC, renal cell carcinoma; SRS, Stereotactic radiosurgery; SRT, stereotactic radiotherapy; AJCC TNM stage, American Joint Committee on Cancer tumor nodal metastatic stage; UCC, urothelial cell carcinoma; WBRT, whole-brain radiotherapy.

diagnosis of brain metastases and brain radiotherapy were not related to neurocognitive impairment (24% vs 14%, p=0.21 and 26% vs 18%, p=0.61). Reporting neurocognitive concerns was not related to neurocognitive impairment on neuropsychological tests (23% vs 10%, p=0.22), but was significantly correlated with higher levels of anxiety and depression (r=−0.455, p<0.001).

Endocrine measurements

Thyroid dysfunction was present in 39 patients (30%), in 34 due to an irAE (26%), and all these patients used thyroid hormone replacement at the study visit. Another 12 patients had either subclinical hypothyroidism or subclinical hyperthyroidism without use of thyroid hormone replacement. Before ICI treatment, three patients had already been diagnosed with primary hypogonadism defined as total testosterone <10 nmol/L and LH>10 U/L, and used testosterone replacement therapy. At the study visit, another 17 men were found to have a total testosterone <10 nmol/L, of whom five had an LH>10 U/L. Six men had an increased LH with a normal testosterone level. 10 out of these 17 patients had NSCLC, resulting in 32% of men with NSCLC having a low testosterone measurement. Prolactin was increased in two patients: one due to pituitary stalk compression by a cyst and the other due to prolactin-producing pituitary microadenoma.

Sexuality

60 men and 33 women completed the GMSEX questionnaire. GMSEX scores were similar for men and women, with mean scores of 22.1 and 24.9, respectively, range: 5–35. 15 men (25%) and 2 women (4%) had a score of 10 or lower, but no significant differences were found in age, body mass index (BMI) and testosterone levels when compared with patients with scores higher than 10. Lower GMSEX score was correlated with higher levels of depressive issues (r=−0.043, p<0.001).

70 men (85%) filled out the IIEF questionnaire. Erectile function subscore had a mean of 11.7 out of 30; 45 (64%) men scored below 14. In our study, men with a score ≥14 (n=25, 36%) were more prone to fill out the GMSEX questionnaire than men with a score below 14 (96% vs 80%) and also seemed more satisfied with their sexual life (GMSEX mean score 30.0 vs 16.9, p<0.01). Men with a lower erectile function score were older, more often had metabolic syndrome, and more often used glucose-lowering drugs. There was no association with testosterone levels (online supplemental table 3).

Cardiovascular risk factors and metabolic syndrome

Hyperlipidemia, hypertension, and diabetes mellitus were present in 94 (71%), 49 (37%) and 24 (18%) patients, respectively. Evaluation of metabolic syndrome was possible in 127 patients. Metabolic syndrome was present in 63 patients (50%), possibly an underestimation due to our strict definition of hypertension. Metabolic syndrome was equally prevalent in women (52%, n=25) and men (48%, n=38), and was similar across cancer types (online supplemental table 4).

6-minute walk test

104 (79%) patients completed the 6MWT, 67 (82%) men and 37 (74%) women. The most common reasons for not performing the test were pain and insufficient time due to logistical reasons. 55 patients (53%) walked the predicted distance or more and almost all patients (102, 97%) walked at least the minimum lower normal. Older age, complete disease response and better QOL were significantly associated with walking more than the expected distance, while a higher HADS score (driven by the depression subscale, p=0.031) was associated with worse performance (online supplemental table 5).

Caregiver quality of life

80 caregivers filled out the QOL questionnaire (table 4). Caregivers had a median age of 64 years (range: 34–83). Mean overall QOL score of caregivers was 106.2 (SD=14.1). Lowest scores were on the positive adaptation subscale: more spiritual feelings (not at all/a little bit, n=66, 83%), more positive outlook on life (not at all/a little bit, n=55, 69%), improved family communication (not at all/a little bit, n=41, 51%), receiving support from friends and neighbors (not at all/a little bit, n=36, 45%), and having a closer relationship with a loved one (not at all/a little bit, n=30, 38%). A low score was also found

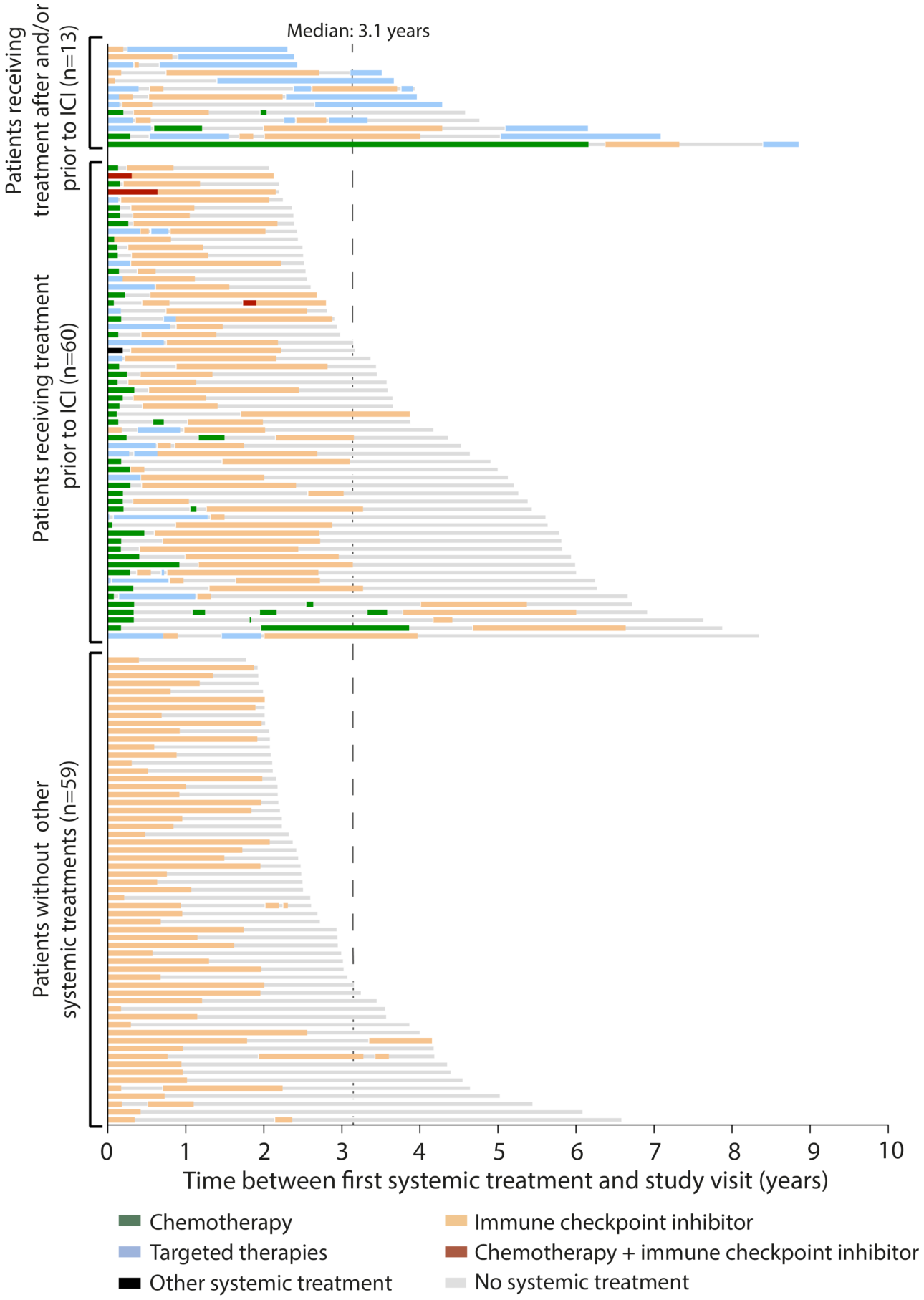

Figure 1 Swimmer plot of all received systemic treatments prior to study visit. ICI, immune checkpoint inhibitors.

Table 2 Prevalence of irAEs

	Any grade, N (%)*	Grade 3/4, N (%)*	Patients with any grade, N (%)†	Patients with ongoing toxicity—any grade, N (%)†
Total	165	25 (15)	95 (72)	62 (47)
Endocrine	54 (33)	2 (1)	48 (36)	48 (36)
Cutaneous	33 (20)	1 (1)	32 (24)	12 (9)
Rheumatic	23 (14)	0	21 (16)	5 (4)
Gastrointestinal	31 (19)	17 (10)	29 (22)	5 (4)
Pulmonary	14 (8)	3 (2)	14 (11)	4 (3)
Ocular	3 (2)	0	3 (2)	1 (1)
Renal	2 (1)	0	2 (2)	0
Hepatic	4 (2)	2 (1)	4 (3)	0
Neurologic	1 (1)	0	1 (1)	1 (1)

Total of 165 irAE of all grades. Of 132 patients, 95 (72%) had at least one irAE. 46 patients had two or more irAE.
*Percentage of total irAEs (165).
†Percentage of total patients (132).
irAE, immune-related adverse event.

on the burden subscale: satisfaction with sexual function (not at all/a little bit, n=31, 39%). Caregivers' QOL score was weakly to moderately and positively associated with patients' global health status (r=0.27, p=0.017) and negatively with depression and anxiety problem (r=−0.485, p<0.001). Patient and caregiver reported QOL differed in 34% of paired patient and caregiver cases (figure 2). No association was observed between caregivers' QOL and survivors' characteristics, including neurocognitive impairment, neurocognitive concerns, or disease status.

DISCUSSION

Our data show that one-quarter of the ICI-treated cancer survivors have lower global health status than the reference population, and that there is a weak to moderate correlation between survivors' and caregivers' QOL. Neurocognitive impairment and concerns are common but not related to QOL. Higher levels of anxiety and depression were significantly associated with lower QOL, sexual satisfaction, and physical condition. Although AEs are frequent, there is no association with lower QOL.

Preserved or even better global health status has also previously been reported in cancer survivors, including patients with melanoma after treatment with ICIs.[10–14 17 40] This may be the result of a different outlook on life, caused by the initial diagnosis of a life-limiting disease and the outcome of being an advanced cancer survivor. This change in perspective may lead to a recalibration of internal standards, which has been associated with a response shift in QOL measures.[41] Cancer survivors may also experience personal growth or increased appreciation of life, both known as positive effects following cancer diagnosis and treatment.[42] However, this does not apply to the entire group, since 28% reported significantly lower QOL. This subgroup with a lower QOL had a higher prevalence of psychological concerns, 48% compared with 11% in the entire group.[23] Previous studies in ICI survivors showed that age[13 18] (both younger and older age) and need for subsequent treatment[13] were related to poorer QOL. We did not find these associations. Differences in methodology (QOL measures used, examined influencing factors, and time of study assessment), and patient population may explain these contradictory results. Despite the 46% prevalence of ICI-related ongoing toxicity at the study visit, this was not correlated with worse QOL, in line with previous studies in patients treated with ICI,[13 18] likely because most persistent irAEs are low grade.[4]

Symptoms of depression and anxiety were both present in 11% of our study population, similar to previous studies in both patients with ICI-treated and non-ICI-treated cancer.[11] This suggests that these symptoms are likely not caused by the ICI treatment but are the result of undergoing and surviving treatment for advanced cancer. In our study, depression and anxiety were the only factors associated with a lower score in all the EORTC QLQ-C30 subscales. Furthermore, they were associated with worse physical performance, lower sexual satisfaction, and worse caregiver QOL. In the follow-up of ICI-treated cancer survivors, explicit attention should be given to screening and treatment of these psychological concerns since this may improve QOL.

A substantial number of survivors had neurocognitive problems, either self-reported (15%) or demonstrated by neuropsychological tests (17%), but these were not correlated to QOL. This prevalence is higher than previously described in the general Dutch population (7% in adults older than 60 years old),[43] but lower than in other studies following ICIs. Two small studies (n≤25) in melanoma survivors after ICI treatment reported prevalences of 20% and 44%, respectively.[9 10] The only study that investigated cognitive impairment in patients with NSCLC

Table 3 Patient quality of life, psychological, neurocognitive, and work-related outcomes

	Total (n=131)	Dutch population
Quality of life (EORTC QLQ-C30)	**Mean (SD)**	**Mean (SD)**
Global health status	80.5 (16.0)	77.4 (19.8)
Physical functioning	85.8 (15.7)*	90.7 (14.9)
Role functioning	80.8 (22.0)*	89.1 (21.5)
Emotional functioning	85.0 (18.8)	82.3 (21.2)
Cognitive functioning	83.3 (17.4)*	90.3 (17.1)
Social functioning	86.4 (20.0)*	91.9 (19.0)
Psychological issues (HADS)	**Total (n=132)**	
	Mean (SD)	
HADS total score	7.14 (5.3)	N/A
At least mild anxiety (≥8), N (%)	15 (11)	
At least mild depression (≥8), N (%)	15 (11)	
Cognitive concerns	**Total (n=79)**	
	Mean (SD)	
Cognitive concerns (FACT-Cog PCI)	62.5 (10.5)	N/A
Cognitive issues present, N (%)†	13 (15)	
Cognitive impairment	**Total (n=132) mean (SD)**	**n<1.5 SD/n<2 SD**
HVLT-R TR (z-score)	−0.24 (1.03)	11/3
HVLT-R DR (z-score)	−0.67 (1.07)	2/10
TMTA (z-score)	0.40 (1.08)	6/4
TMTB (z-score)	0.29 (1.18)	8/3
COWA (z-score)	−0.44 (1.05)	9/2
Total digit span test (z-score)	0.49 (1.12)	6/6
Overall neurocognitive impairment, N (%)	22 (16.7)	
Work status	**Total (n=132)**	
Working at the start of ICI, N (%)	77 (58)	
Working at time of study visit, N (%)	41 (31)	

*p<0.01.
†FACT-Cog PCI<54.[26]
COWA, Controlled Oral Word Association; EORTC QLQ-C30, European Organization for the Research and Treatment of Cancer Quality-of-Life Questionnaire ; FACT-Cog PCI, Functional Assessment of Cancer Therapy-Cognitive Function V.3 - Perceived Cognitive Impairment; HADS, Hospital Anxiety and Depression Scale; HVLT-R DR, Hopkins Verbal Learning Test-Revised delayed recall; HVLT-R TR, Hopkins Verbal Learning Test-Revised total recall; ICI, immune checkpoint inhibitor; TMT, Trail Making Test.

after 1 year of ICI treatment reported a prevalence of 43% in the patients, but also a high rate of 23% in the control group.[44] Another study showed a prevalence of 26% in patients with NSCLC treated with ICI or another systemic therapy.[45] Neurocognitive impairment following ICI treatment may result from different mechanisms, such as direct damage due to recognition of autoantigens or T-cell activity or by enhancing a pre-existing subclinical autoimmune response against the nervous system.[46] Hormonal changes, for example, the absence of a cortisol response to a physiological stressor, have been associated with impaired memory in patients with breast cancer.[47] A study proposed that immune-mediated hypophysitis could lead to cognitive impairment,[10] but in our cohort, none of the 15 patients with hypophysitis developed cognitive impairment. While neurocognitive problems may negatively impact patients' routines, we did not find a worse QOL in patients with cognitive impairment.

At the study visit, 34 patients (26%) had thyroid dysfunction due to irAEs, consistent with the previously reported 33% incidence.[1] Thyroid dysfunction onset typically occurs early in treatment (median time 14.5 weeks).[48] It leads mainly to hypothyroidism, sometimes preceded by a hyperthyroidism phase. Since our study measurements were taken at least 2 years after the start of ICI treatment, it is expected that all patients had passed any potential hyperthyroid phase. While recovery of thyroid function has been described,[49] all 34 patients in our cohort received hormone replacement therapy. The American Society of Clinical Oncology guidelines suggest tapering

Table 4 Caregiver characteristics and quality of life outcomes

	Total (n=80)
Age, median (range)	64 (34–83)
Relation to patient, N (%)	
Partner	78 (98)
Child	2 (2)
Quality of life (CQOLC), mean (SD)	
Total score (0–140)	106.2 (14.1)
Caregiver burden (0–56)	43.9 (9.5)
Disruptiveness (0–36)	32.2 (4.1)
Positive adaptation (0–32)	14.8 (6.2)
Financial burden (0–12)	11.4 (1.5)

CQOLC, Caregiver Quality of Life Index-Cancer.

or discontinuation of hormone replacement therapy under close follow-up in patients with a low TSH, as this may indicate overtreatment or recovery of thyroid function.[48] The Dutch guidelines mention that this can be considered, but our experience shows that this does not occur very often. Further studies are needed to clarify the success rates of stopping hormone replacement and to identify which patients are candidates for this approach.

We found that almost one-quarter of men had a total testosterone level below 10 nmol/L, measured once during the study visit, with a higher prevalence in the patients with NSCLC. ICI treatment can induce hypophysitis and secondary hypogonadism, but we did not observe this in our population. Immune-mediated primary hypogonadism is an alternative explanation.[50] Low testosterone was not correlated with a lower GMSEX score or erectile dysfunction. However, 64% of men had at least a moderate level of erectile dysfunction, compared with 13% in the general Dutch population.[51] Erectile dysfunction was associated with commonly described risk factors such as older age, diabetes mellitus and metabolic syndrome, and was linked to lower sexual satisfaction. The sexual satisfaction found within our cohort is similar to earlier studies in patients with cancer,[52] but lower than in the general population.[53] Additionally, the caregiver's evaluation also showed that 39% of partners are unsatisfied with their own sexual functioning. Sexual issues are common in cancer survivors[52] and deserve a more prominent place in survivorship research and care.

Half of the survivors fulfilled the criteria for metabolic syndrome, a higher prevalence than the general Dutch

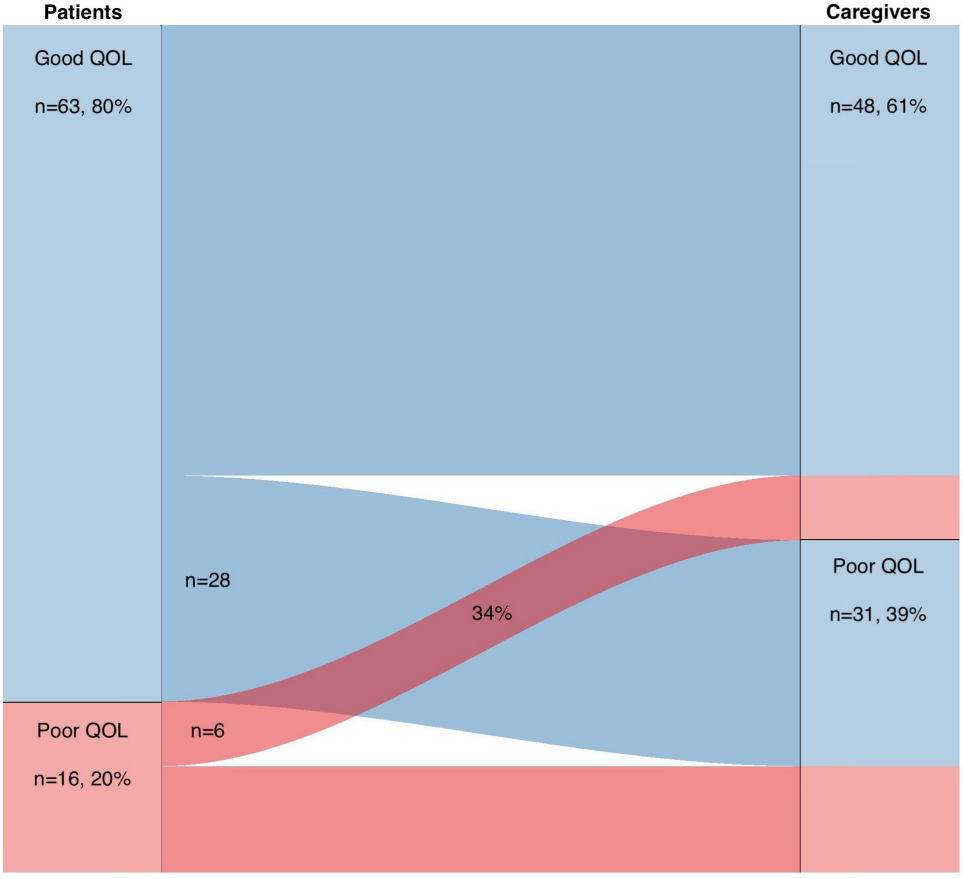

Figure 2 Paired patient and caregiver QOL. Poor QOL defined as: ≥10 points lower than group mean on European Organization for the Research and Treatment of Cancer Quality-of-Life Questionnaire global health scale for survivors; below the group mean of Caregiver Quality of Life Index-Cancer score for caregivers. QOL, quality of life.

population (29% in individuals older than 70 years),[54] and 65% of our cohort were at least overweight. This higher prevalence of metabolic syndrome may result from shared risk factors with cancer. Interestingly, it has been described that overweight and metabolic syndrome are associated with better overall survival in patients receiving ICI treatment (obesity paradox).[55] One explanation for the obesity paradox is that low-grade inflammation, especially visceral fat-induced, leads to enhanced T-cell activity and, therefore, potentially a higher ICI efficacy. However, there are essential confounders for this phenomenon; for example, a lower BMI may result from a more aggressive tumor or due to active smoking, what is related to a poorer prognosis.[56] Another explanation for the high prevalence of cardiovascular risk factors is perhaps the lack of attention for secondary prevention in patients facing an advanced cancer diagnosis and having a very uncertain prognosis. Cardiovascular risk management should be resumed in survivors with good response since they may live for many years and gain benefit from usual preventive treatment.

This is the first study that formally evaluated the QOL of caregivers of cancer survivors treated with ICI. Mean CQOLC in our cohort was better than earlier described in patients undergoing active treatment,[57] and similar to caregivers from head and neck cancer survivors 2 years after treatment,[58] and to caregivers of survivors with good performance status.[29] Despite this relatively positive outcome, we found different survivor and caregiver QOL in one-third of our group. Shahi *et al*[59] described a positive association between caregivers and patients' QOL undergoing radiotherapy. This contrast may result from differences in the studied population (patients undergoing treatment vs 2-year survivors) or methodology (group size or use of mean split). Although further characterization of this group is required, our results highlight the importance of separately assessing caregiver's QOL to identify their needs. This data underscores the importance of tailored survivorship care, not only supporting patients but also addressing the needs of their informal caregivers.

The increasing use of ICIs in adjuvant and neoadjuvant settings raises questions about the long-term effects in these populations. Patient characteristics, extent of disease and treatment duration differ between metastatic and (neo)adjuvant settings, and therefore our findings may not translate directly to these populations. However, it is known that toxicity rates (irAE grade 3–5) of ICI can be as high as 46% in the adjuvant setting and 41% in the neoadjuvant setting.[2 3] Some irAEs are permanent and may require lifelong therapy, which can negatively impact the QOL of patients and their caregivers. Since the long-term benefit in terms of overall survival of (neo)adjuvant ICI treatment remains unclear, potential long-term toxicity is important to consider during shared decision-making in clinical practice. Novel (longitudinal) studies addressing long-term toxicity and psychosocial issues in these populations are needed since the treatment and toxicity of these patients differ from those with advanced cancer.

We have comprehensively assessed QOL, neurocognitive function, sexuality, and comorbidities in long-term advanced cancer survivors after ICI treatment. An important strength of our study is that we have also separately assessed the caregiver QOL. One of the main limitations of our study is its cross-sectional design, which restricts the evaluation of the course of these findings over time. The still relatively small group of patients precludes further subgroup analyses. Furthermore, the cancer survivors were required to attend the study visit in person. Therefore, survivors with a relatively good performance status, including disease control, are probably over-represented in our cohort. On the other hand, part of our population had been treated with other types of systemic therapy, potentially increasing symptom burden. Longitudinal studies with larger cohorts are required to provide adequate survivorship care to this emerging group.

In conclusion, advanced cancer survivors treated with ICI generally have good QOL. However, subgroups exist with lower QOL associated with symptoms of depression and anxiety. These symptoms may influence sexual health and caregiver QOL and should be screened for in ICI survivors. Screening and treatment should also be resumed for cardiovascular health since ICI survivors may live for many years.

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Contributors JN, WC and ACE had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. JN designed the study. IB trained ACE and KCvH in neurocognitive assessment. ACE, RDH, KCvH and WC collected the data. WC and ACE analyzed and interpreted the data. WC, ACE and JN drafted the manuscript. All authors contributed to patient recruitment and provided critical revisions, gave final approval and agreed to be accountable for the work. JN is the guarantor of the overall content.

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