Thalassemia major (TM) is a lifelong inherited medical condition that is difficult and expensive to treat. Therapy typically entails regular blood transfusion and iron chelation. Currently, only bone marrow transplantation is curative, although there are ongoing gene therapy trials. Before the use of the iron-chelating drug deferoxamine, in the late 1960s, the condition almost invariably resulted in death by the age of 20 due to iron overload. However, with the emergence of iron chelation therapy, it is now possible to extend the lifespan of patients. Galanello and Origa stated that “1.5% of the global population, (~80 to 90 million people), are carriers of beta-thalassemia, with about 60 000 symptomatic individuals born annually, the great majority of whom live in the developing world”, specifically indicating those populations residing in the Eastern Mediterranean region, subcontinental regions, and equatorial regions of Asia, Africa, and Central Asia.

Various studies have shed light on the neurological complications of thalassemia. One...
hypothesis suggests that neurological complications are possibly due to thromboembolic events, albeit more commonly found in thalassemia intermedia (TI). Borgna Pignatti et al,\(^4\) identified the thromboembolic events as important precursors to the development of neurobehavioural impairment. TM patients with thromboembolic events were also more likely to have heart disease, diabetes, and chronic liver disease. An Italian study on individuals with TM and TI found that, compared to controls, no significant difference in brain and intracranial vascular changes was present. However, they did find cognitive impairment and increased psychological disorders in TM patients compared to those with TI.\(^5\) Raz et al,\(^6\) have conducted electrophysiological studies and compared the results to healthy controls. Individuals with TM performed poorly on indices of neuropsychological functioning and were concurrently shown to have attenuated cortical arousal in brain regions critically associated with higher cognitive functioning. In addition to overt neurological complications and cortical arousal, there is evidence to suggest that people with thalassemia are likely to have subtle yet intransigent cognitive impairment.\(^7\)–\(^9\) The majority of the neuropsychological studies in people with TM, with a few exceptions, have been limited to the Euro-American population, though this condition is more prevalent in North African, Middle Eastern, and Asian countries.\(^10\)

In addition to intellectual capacity, neuropsychological functioning constitutes attention and concentration, memory functioning, and other higher indices. While there is a variety of studies on psychosocial functioning examining the quality of life in people with TM,\(^11\) there is a lack of studies on neuropsychological functioning in adult patients with TM. Such an undertaking is likely to audit whether functionality has a direct bearing on cognition. Among many and varied psychosocial dysfunctions, studies have suggested that impaired neuropsychological functioning tends to have a direct bearing on the quality of life and meaningful existence in people with hematologic diseases.\(^12\)

We sought to examine the neuropsychological status of Omanis with TM undergoing regular follow-up at a tertiary care hospital in Oman. As normative data for neuropsychological batteries have often been lacking in Oman, healthy control subjects were utilized to tease out how individuals with TM fared in comparison.\(^13\) A related aim was to examine the clinical, demographic, and psychological factors associated with neuropsychological performance.

**METHODS**

Over 200 patients with TM are currently followed-up in both adult and pediatric daycare centers of Sultan Qaboos University Hospital (SQUH), Muscat, Oman. It is important to note that SQUH has a national catchment area.

Omani nationals between the ages of 18 and 44 years old were included in the study. The upper limit of the age range (≤ 44 years) was based on the rationale that people > 45 years are likely to have subtle cognitive decline and were therefore excluded from the study.\(^14\)

To further consolidate homogeneity of the cohort, the participants were required not to endorse pervasive and persistent features of cognitive decline as defined by the Montreal Cognitive Assessment based on normative data from the Arabian Gulf.\(^15\) All the psychometric evaluations for the study were conducted and performed by a qualified neuropsychologist.

All patients were on a regular transfusion program to maintain hemoglobin > 9 g/dL and taking regular iron chelation therapy. Non-transfusion dependent patients were excluded. Potential participants with documented evidence of intellectual disability or pervasive and persistent psychiatric disorders were also excluded. A total of 104 patients fulfilled these criteria; 28 were finally able to complete the protracted psychometric evaluation.

Oman has yet to develop normative data for neuropsychological batteries.\(^13\) In line with other studies that have examined neuropsychological status among people with TM,\(^11\)\(^16\) healthy volunteers were invited to participate in this study as a comparative group. The healthy controls, matched for sociodemographic background, were recruited amongst the staff of SQU. The staff selection represents a minimal selection bias (n = 39). Inclusion criteria for the healthy controls included those with a clean bill of health and no evidence of a persistent and pervasive history of medical, psychiatric, or neurological complications that resulted in seeking medical attention. This was verbally corroborated for all healthy volunteers.
Raven’s Progressive Matrices was employed to tap into nonverbal reasoning ability, a measure orthogonal to linguistic and scholastic skills. It is comprised of 60 items grouped into five sets; each item consists of a pattern with one part removed and six and eight inserts pictured, each of which contains the appropriate missing part. The participants were required to point to what they perceived to be the correct insert for each pattern. This test measures reasoning ability or the ‘meaning-making’ component of Spearman’s fluid intelligence, which is often referred to as general intelligence.

Digit Span derived from the Wechsler Adult Intelligence Scale was used to tap into the variation of attention and concentration. Both versions of Digit Span—digit span forward and digit span backward—were used and scored separately. There is evidence to suggest that these two versions measure two different domains.

Participants’ ability to learn and remember was gauged using the California Verbal Learning Test (CVLT), which consisted of 16 shopping list items. This test is designed to record correct recalling or perseverative errors. Three indices are used: (1) immediate recall operationalized here as short-term memory, (2) long delay free recall or long-term memory assessed 25 minutes after completion of the short-term memory test, and (3) perseverative errors, which are examinee ‘created’ items that are absent from the list.

Executive functioning constitutes an amalgamation of complex cognitive processes, including planning, working memory, and domains that reflect the temporal organization of behavior and self-regulation. We employed two executive functioning measures: the verbal fluency test/Controlled Oral Word Association Test (COWAT) and Trail Making Test (TMT). The integrity of verbal fluency or phonological fluency was solicited using the COWAT. The participant is required to generate as many different words as possible, starting with three specific letters with one minute allowed per letter. The letters were taa, raa, and waaw, which were previously ascertained to have heuristic value in the Arabic language. The total score for COWAT was thus the total number of different acceptable words produced across the three 60-second periods. There is vast literature suggesting that the TMT solicits the integrity of executive functioning and psychomotor speed. The TMT has two versions of the test—Form A and Form B. We utilized Form B, whereby the examinee was asked to draw a line to connect, in alternating sequence, the digits 1 through 12 and the letters A through L. The performance was scored in seconds.

The affective range was solicited using the Hospital Anxiety and Depression Scale (HADS). HADS is a 14-item symptom checklist designed to tap into the presence of anxiety and depression with seven items for each type. We used the Arabic version of the scale. A cut-off ≥ 8 is considered to constitute caseness for either depression or anxiety.

To fulfill the study objective, various covariates were garnered directly from the participants or medical records. The study utilized sociodemographic factors and clinical variables. The clinical variables are detailed as part of the inclusion criteria.

Power analysis is based on one of the outcomes, the indices of learning and remembering (CVLT), and comparing two groups (control vs. TM) using a t-test. We expected the effect sizes between the two groups to range from 0.70 to 0.75 with a ratio of 1:0.7 (control: TM). The required sample size ranged from 62 (control vs. TM = 36 vs. 26) to 70 (control vs. TM = 41 vs. 29) at 80% power with a 5% level of significance (nQuery Advisor v6.01). At the end of the study period, 67 adult participants (control = 39, TM = 28) were recruited, which was within the range of our expected sample sizes.

We used SPSS Statistics (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.) for data analysis. The results of those associated with the two groups (TM vs. control) were displayed using descriptive statistics. First, univariate analysis was used, and sociodemographic and clinical variables were evaluated with the chi-square test or t-test to reveal association or difference in two groups. Following this, multivariate log-linear (Poisson) analysis was used where groups (TM vs. control), anxiety, and depression were the factor variables and psychological scores were the covariate variables. The level of significance was set at 5%.

Ethical approval was granted by the local institutional review board at the College of Medicine and Health Sciences at SQU, Muscat, Oman (Ref. No. SQU-EC/027/18, MREC #1659). Written informed consent was collected from all participants. The study was conducted per the Declaration of Helsinki and the American
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Psychological Association regarding ethical human research, including confidentiality, privacy, and data management.

**RESULTS**

Our study included 28 adult patients with TM (mean age 30.0±6.5 years) and 39 healthy controls (mean age 29.2±6.1 years) [Table 1].

The patient cohorts did not differ in their distribution of age ($p = 0.610$), and gender ($p = 0.137$). As expected, the two groups differed in the presently defined medical outcome.

The data suggest that the two cohorts did not differ in their performance on the indices of cognition, current nonverbal reasoning ability. However, with regard to the other domains of cognition such as attention and concentration, learning and remembering, verbal fluency, and executive functioning, the TM group had significantly different scores from healthy controls. In the multivariate (log-linear) analysis, the variables that were significant at 5% in the univariate analysis were used for further analysis. The analysis showed that TM patients were more likely to have anxiety (odds ratio (OR) = 5.82, $p < 0.001$) and depression (OR = 7.75, $p < 0.001$) when compared to healthy controls. In addition, TM patients had lower short-term memory capacity ($\beta = 0.989$, $p < 0.001$), verbal fluency scores ($\beta = 0.279$, $p = 0.003$), and verbal and auditory attention (digit

| Variables | Thalassemia major | Control | Univariate | Multivariate |
|-----------|-------------------|---------|------------|--------------|
|           | Yes (n = 28)      | No (n = 39) | Statistics | $p$-value | Statistics | $p$-value |
| Demographic |                   |         |            |          |           |          |
| Gender    |                   |         |            |          |           |          |
| Female    | 18 (64.3)         | 17 (43.6) | 2.798$^a$ | 0.137     |           |          |
| Male      | 10 (35.7)         | 22 (56.4) |            |           |           |          |
| Age, years, mean ± SD | 30.0 ± 6.5        | 29.2 ± 6.1 | 0.513$^c$ | 0.610     |           |          |
| Cognition |                   |         |            |          |           |          |
| Current reasoning ability |             |         |            |          |           |          |
| Attention and concentration |             |         |            |          |           |          |
| Raven’s progressive matrices | 25.6 ± 3.7       | 27.5 ± 4.6 | 1.753$^c$ | 0.084     |           |          |
| Digit span forward | 5.8 ± 1.9        | 9.0 ± 1.0 | 7.882$^c$ | < 0.001   | 0.903     | 0.002    |
| Digit span backward | 4.1 ± 1.6        | 8.1 ± 0.9 | 11.467$^c$ | < 0.001   | -0.722    | 0.587    |
| Learning and remembering |             |         |            |          |           |          |
| CVLT-short term memory | 16.0 ± 5.3       | 22.2 ± 3.1 | 5.552$^c$ | < 0.001   | 0.989     | < 0.001  |
| CVLT-long term memory | 9.9 ± 3.0        | 20.5 ± 3.4 | 12.949$^b$ | < 0.001   | -0.189    | 0.304    |
| CVLT-perseverative errors | 3.1 ± 2.6        | 0.2 ± 0.8 | 5.461$^c$ | < 0.001   | 0.488     | 0.264    |
| Executive function |             |         |            |          |           |          |
| COWAT      | 14.3 ± 5.1        | 20.9 ± 3.0 | 6.039$^c$ | < 0.001   | 0.279     | 0.003    |
| TMT        | 135.3 ± 64.1      | 88.6 ± 7.3 | 3.833$^c$ | 0.001     | -0.003    | 0.920    |
| Affective range |             |         |            |          |           |          |
| HADS-D     | Yes | 9 (32.1) | 2 (5.1) | 8.763$^d$ | 0.006 | 7.752 | < 0.001 |
| No        | 19 (67.9) | 37 (94.9) |            |           |           |          |
| HADS-A     | Yes | 10 (35.7) | 5 (12.8) | 3.778$^c$ | 0.027 | 5.818 | < 0.001 |
| No        | 18 (64.3) | 34 (87.2) |            |           |           |          |

*Chi square, †odds ratio, ‡statistics.

SD: standard deviation; CVLT: California Verbal Learning Test; COWAT: Controlled Oral Word Association Test; TMT: Trail Making Test; HADS-A: Hospital anxiety and depression scale, 8+ anxiety; HADS-D: Hospital anxiety and depression scale, 8+ depressed.
span forward) scores ($\beta = 0.903, p = 0.002$) when compared to healthy controls.

**DISCUSSION**

Like its counterpart, sickle cell disease, thalassemia is widely prevalent among people living in temperate and equatorial parts of the world, including the Arabian Peninsula. The prevalence rate of the beta-thalassemia gene in Oman has been estimated to be 2%.

Despite its multimorbidity, people with TM have greatly benefitted from better overall management of disease; specifically, adequate red blood cell transfusion, iron chelation, and complications management.

Although a significant number of people with TM are experiencing a longer life span, some persist with poor but subtle neurological, psychosocial, and cognitive outcomes. While there is extensive literature on neurological and psychosocial factors, scant attention has been paid to the neuropsychological status of adults with TM. Among the many studies that have emerged on the cognitive status of people with TM, the majority have focused on children or a cohort constituting the heterogeneous spectrum of beta-thalassemia and sickle cell disease. To the best of our knowledge, despite its wide prevalence, the neuropsychological status of adults with TM is under-researched in the Arabian Gulf population.

In Oman, the benefit of comprehensive medical care for people with TM is a recent phenomenon, and most older patients did not receive comprehensive care compared to their younger counterparts due to the initial unavailability of services. Unlike the younger age groups, the older Omani cohort has hepatitis C virus positivity, splenectomy, diabetes, and hypogonadism.

In developed countries, there are now TM patients in their fifth and sixth decades. In Oman, there are now many patients aged 20–40. With the improvement of life expectancy and quality of life, more patients are acclimatizing to more ‘normal’ circumstances such as working, getting married, and looking forward to a ‘normal’ life. Exploring their neurocognitive functionality is therefore important. Thus, to address this issue and lay the groundwork for further scrutiny, this study examined neuropsychological functioning among adult Omanis with TM. A related aim was to explore the factors associated with neuropsychological performance.

In our study, the individuals with TM and the healthy control group did not differ on variables such as age, gender, or intellectual capacity, determined using a nonverbal intelligence quotient test (Raven’s Progressive Matrices Test). The presently observed preservation of intellectual capacity appears to distinguish the current study from the rest, where patients with beta-TM were reported to have lower total performance intellectual capacity when compared with controls on nonverbal batteries of the Wechsler Adult Intelligence Scale. Although our study does suggest that the intellectual capacity of people with TM differs from healthy controls ($25.6\pm3.7$ vs. $27.5\pm4.6$), the difference did not reach significance. More studies are therefore warranted to disentangle this issue since intellectual capacity is known to critically predict one’s academic performance.

The inclusion criteria only considered those with adequate cognition to minimize the impact of outliers in terms of cognitive capacity. Among the neuropsychological domains that showed significantly different results between the two groups were the indices of attention and concentration, learning and remembering, and executive function. A study from Italy compared beta-TM patients to healthy controls. Their study explored comparable neuropsychological domains but different neuropsychological batteries. Their results suggested that attentional capacity, memory, and executive function were significantly different from healthy controls. Other more recent studies are congruent with the present observations.

In our study, multivariate (log-linear) analysis was employed to tease out the most parsimonious factors that account for the observed neuropsychological functioning in individuals with TM. Such an undertaking has the potential to suggest the neuropsychological phenotypes of people with TM. The present data indicate that executive functioning, tapped into by COWAT, and related domains such as working memory/temporal organization of behavior (digit forwards and CVLT-short term memory) are neuropsychological phenotypes of people with TM. As most of the studies on TM are among children and adolescents, it is difficult to compare those results with our adult population. However, among the adult population with TM,
the main neuropsychological deficits fall within the executive-working memory spectrum. The neural substrate for the executive-working memory spectrum should be explored using a functional brain scan.

A related aim of this study was to examine which neuropsychological domains and affective ranges had a direct bearing on the observed neuropsychological performance. Our data suggest that affective ranges have the potential to impinge cognition. For this study, the HADS was employed to solicit the presence of affective ranges. HADS was developed to quantify a non-psychiatric type of emotional burden among people with chronic illness.25

Previous studies have suggested that psychiatric-like mood disorders are common among children with TM.34 Since both anxiety and depression are high in chronic clinical and the general population, it is essential to compare them to healthy controls. However, when the study from Italy by Monastero et al., compared the rate of depression and anxiety among the two groups, they did not differ. Our study took a different path by examining whether affective ranges impacted neuropsychological functioning. The study appears to suggest that both anxiety and depression have a direct bearing on the neuropsychological status. On one hand, this study seems to add to the complexity of the relationship between affective ranges and cognition.5 On the other hand, if this study were to withstand further empirical scrutiny, it would merit mitigation measures to ameliorate affective ranges. There are ample evidence-based psychotherapeutic techniques available for affective dysfunction. More studies are therefore warranted.

There are certainly some limitations common to studies of this sort, some of which will be highlighted below. Firstly, the generalization of this study could be affected by the small sample size. This is partly linked to the study criteria that limited the participant pool to a homogenous cohort of TM within a defined age group. Secondly, existing literature has employed divergent neurocognitive measures.

**CONCLUSION**

Our study employed the most commonly used neuropsychological batteries. The results showed no impairment of intellectual capacity in TM patients. However, there were deficits in the domains of executive function and working memory compared to controls. Further studies are needed to identify TM-specific neuropsychological phenotypes and ensure that specific neuropsychological batteries are developed to facilitate comparison across studies.

**Disclosure**

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