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ORIGINAL ARTICLE

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Clinical, neuroimaging, and behavioural risk factors for neurocognitive impairment in Chinese patients with haemophilia: A multicentre study

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Abstract

Background: Few studies have evaluated the impact of subclinical microstructural changes and psychosocial factors on cognitive function in patients with haemophilia.

Objectives: To determine the prevalence and characteristics of cognitive impairment in patients with haemophilia, and identify associated risk factors.

Methods: We recruited haemophilia A or B patients who were aged ≥10 years old from three public hospitals in Hong Kong. A neurocognitive battery was administered to evaluate their attention, memory, processing speed and cognitive flexibility performances. They also underwent magnetic resonance imaging to identify cerebral microbleeds. Validated self-reported questionnaires were administered to assess their mental health status and adherence to prophylactic treatment. General linear modelling was used to investigate the association of neurocognitive outcomes with risks factors, adjusting for age and education attainment.

Results: Forty-two patients were recruited (median age 32.0 years; 78.6% haemophilia A; 80.9% moderate-to-severe disease). Six patients (14.3%) had developed cerebral microbleeds. A subgroup of patients demonstrated impairments in cognitive flexibility (30.9%) and motor processing speed (26.2%). Hemarthrosis in the previous year was associated with worse attention (Estimate = 7.62, 95% CI: 1.92–15.33; p = .049) and cognitive flexibility (Estimate = 8.64, 95% CI: 2.52–13.29; p = .043). Depressive (Estimate = 0.22, 95% CI: 0.10–0.55; p = .023) and anxiety (Estimate = 0.26, 95% CI: 0.19–0.41; p = .0069) symptoms were associated with inattentiveness. Among patients receiving prophylactic treatment (71.4%), medication adherence was positively correlated with cognitive flexibility (p = .037).

Conclusion: A substantial proportion of patients with haemophilia demonstrated cognitive impairment, particularly higher-order thinking skills. Screening for cognitive deficits should be incorporated into routine care. Future studies should evaluate the association of neurocognitive outcomes with occupational/vocational outcomes.

KEYWORDS
cerebral microbleed, cognitive function, haemophilia, neuroimaging, psychological

1 | INTRODUCTION

Intracranial haemorrhage is considered one of the most serious consequences of haemophilia and is associated with significant neurological impairments.[1,2] Studies have reported that clinical intracranial haemorrhage can lead to worse executive function among paediatric patients with haemophilia, compared to matched healthy controls.[3] Differences in IQ, visuospatial skills, and fine motor dexterity were also observed in a study comparing haemophilia patients with and without a history of intracranial haemorrhage.[4]

While clinical intracranial haemorrhage is uncommon among patients with haemophilia who receive adequate treatment, silent cerebral microbleeds can still occur.[5,6] Cerebral microbleeds are small bleeding events in the brain that appear as hypointense lesions on gradient echo magnetic resonance imaging (MRI).[7] Two studies have evaluated cerebral microbleeds in patients with haemophilia using MRI, reporting frequencies ranging from 7% to 35%.[5,6] Limited evidence has suggested that, despite a lack of clinical symptoms, subclinical microstructural changes in the brain might contribute to various clinically relevant sequelae, such as vascular cognitive impairment and behavioural symptoms.[5,8,9] Moreover, studies have reported the significant impact of haemophilia on patients' mental health and social well-being,[10,11] but few have evaluated the impact of these psychosocial factors on cognitive function in patients with haemophilia.

Currently, there are ~220 patients diagnosed with mild-to-severe haemophilia under the care of public hospitals in Hong Kong.[12,13] The objectives of this study were to determine the prevalence and characteristics of cognitive impairment in patients with haemophilia, and identify associated risk factors in this population.

2 | METHODS

2.1 | Study design

This was a multicentred, cross-sectional study. Between January 2021 and June 2022, the research procedures were conducted prospectively at three public hospitals in the North Territories region of Hong Kong: the Prince of Wales Hospital, Princess Margaret Hospital, and Tuen Mun Hospital. Eligible patients were also recruited via the Hong Kong Haemophilia Society, the only local non-governmental organization that serves patients with haemophilia. This study was approved by The Chinese University of Hong Kong and New Territories East Cluster (Ref: 2019—023). All participants provided written consent.

2.2 | Study population

The inclusion criteria were patients who were (1) diagnosed with haemophilia A or B, (2) aged ≥10 years old, and (3) understood written and spoken Cantonese or Mandarin. Participants were excluded if they had pre-existing neurological or developmental conditions known to limit cognitive function, such as Down's syndrome or autism spectrum disorder.

2.3 | Neurocognitive outcomes

Performance-based neurocognitive tests were administered by trained professionals to assess specific aspects of neurocognitive function, including: (1) attention (Conners' Continuous Performance Test-III),[14]

(2) immediate and delayed memory recall (Modified Taylor Complex Figure),[15] (3) visuomotor processing speed (Trail Making Test Part A and Grooved Pegboard Test),[16] and (4) cognitive flexibility (Trail Making Test Part B).[16] Neurocognitive outcomes were transformed into age-adjusted T-scores (mean = 50, standard deviation [SD] = 10.0) using published age- and sex- matched normative data (Supplement 1).[14–18]

2.4 | Neuroimaging

All participants underwent MR imaging of the brain in a 3T MR scanner (Philips Achieva 3.0T, X Series) using standardized sequences, including axial T2-weighted, fluid attenuated inversion recovery (FLAIR) and susceptibility-weighted imaging (SWI). An experienced paediatric radiologist blinded to the subjects' disease severity and cognitive outcomes reviewed the MR images via the PACS system (Carestream Solutions). Microbleeds were defined as round or ovoid hypointense, grey or white matter lesions on SWI.[7] The signal should be devoid of signal hyperintensity on T1- or T2-weighted sequences and distinct from other potential mimics such as iron or calcium deposits or cavernous malformation.[7] Various thresholds have been used for defining microbleeds; we used the definition of ≤5 mm, which is adopted by other imaging studies.[5,7,19] Brain microbleeds were categorized as lobar[5,9,20,21] (cortical grey and subcortical or periventricular white matter), deep grey matter[22] (basal ganglia and thalamus and the white matter of the corpus callosum and internal, external, and extreme capsule), or infratentorial[20,21] (brain stem and cerebellum), as previous cognitive studies have correlated neuroimaging parameters on these structures with functional impairment. Other radiographic abnormalities such as infarcts or white matter signal changes were also recorded if present.

2.5 | Behavioural covariates

On the day of the neuroimaging and neurocognitive assessment, the mental health status of each participant was assessed using the Depression, Anxiety and Stress Scales-21 items (DASS-21).[23] The DASS-21 evaluates the severity of self-reported depression, anxiety, and stress levels. It has been validated in the Chinese population with satisfactory reliability and latent structure.[24] A higher score is indicative of worse symptoms.

Among patients receiving prophylactic clotting factors, treatment adherence was evaluated using the Validated haemophilia Regimen Treatment Adherence Scale-Prophylaxis (VERITAS-Pro) questionnaire.[25] This is a 24-item questionnaire that quantifies self-reported compliance and considers the multifactorial nature of non-compliance. The score can range from 24 (most adherent) to 120 (least adherent). The traditional Chinese version of the VERITAS-Pro questionnaire has previously been used and validated for use in patients with haemophilia in Hong Kong.[26]

2.6 | Clinical and treatment covariates

Consistent with international recommendations, prophylactic factor infusion (2-3 times per week) for patients diagnosed with moderate-to-severe haemophilia has become the standard of care in Hong Kong.[12] Both factor VIII and factor IX concentrates are available as specialist items under Hong Kong's public health care at no additional cost to patients. As recombinant products are only registered in Hong Kong in late 2022, almost all patients with haemophilia are treated with purified plasma-derived factor concentrates during the study period. A minority of patients who had developed inhibitors received bypassing agents.

Clinical data (haemophilia severity, hemarthrosis at target joint(s), intracranial bleeding events, comorbidities, and weight) were extracted from electronic health records. Treatment data (types of factor concentrates and frequency of prophylaxis) was extracted from dispensing records.

Sociodemographic factors (education level, employment, and personal income) were assessed using patient/proxy interviews.

2.7 | Sample size

The primary measure was the difference in mean cognitive scores between patients with haemophilia and published data of healthy individuals (mean T-score = 50, SD = 10). Published mean differences in cognitive scores among the latter population have ranged from 1.0 to 2.5 SDs.[4,5,27,28] Conservatively, to detect a 1.0 SD difference in scores between patients and controls with an α of 0.05 and power of 0.8, a sample size of 42 patients was required.

2.8 | Statistical analysis

Sample characteristics and outcome measures are summarized using descriptive statistics, stratified by age group (paediatrics: age < 18 years old; young adults: 18 to < 40 years old; and older adults: age > 40 years old). The characteristics of patients presenting with cerebral microbleeds on neuroimaging are also presented descriptively.

One-sample t-tests were used to compare patient and control populations. False discovery rates (FDRs) were used to account for multiple testing of cognitive measures.[29] Measures for which the patients differed from the normative samples after correcting for FDR were included in subsequent multivariable analyses. T-scores were calculated for each measure such that T-scores ≥1.0 SD and ≥1.5 SD represented mild and moderate-to-severe impairment compared to the age-adjusted controls. As a past history of intracranial bleeding is a known risk factor of cognitive impairment,[30,31] we reported the rates of cognitive impairment in overall cohort, as well as stratified by history of intracranial bleeding.

Multivariable general linear models were constructed to identify factors associated with cognitive scores, after adjusting for age and educational level. Based on both the literature and clinical consensus,

TABLE 1 Demographics and clinical characteristics of study cohort.

Sociodemographic variables	Total ($n = 42$) n (%)	Paediatrics (aged < 18 years) ($n = 11$)	Young adults (aged 18 to < 40 years) ($n = 22$)	Adults (aged > 40 years) ($n = 9$)
Age (years) median [IQR]	32.0	15.6	33.0	55.2
	[16.8–39.7]	[13.4–16.6]	[26.4–36.9]	[50.9–56.8]
Highest Education Attainment				
Secondary school or below	20 (47.6)	8 (72.7)	6 (27.3)	6 (66.7)
Post-secondary school or above	22 (52.4)	3 (27.3)	16 (72.7)	3 (33.3)
Employment				
Student	13 (31.0)	11 (100)	2 (9.1)	0
Employed	22 (52.3)	0 (0)	17 (77.3)	5 (62.5)
Unemployed/retired	7 (16.7)	0 (0)	3 (13.6)	4 (44.4)
Personal monthly income (Employed adults only) ($n = 22$)				
<HKD 10,000	3 (13.6)		3 (17.7)	0 (0)
HKD 10,000–19,999	7 (31.8)		7 (41.2)	0 (0)
HKD 20,000–29,999	4 (18.3)		3 (17.6)	1 (33.3)
HKD 30,000–39,999	5 (22.7)		2 (11.8)	3 (33.3)
≥40,000	3 (13.6)	NA	2 (11.8)	1 (33.3)
Clinical variables				
Diagnosis				
Haemophilia A	33 (78.6)	10 (72.7)	18 (81.8)	5 (55.6)
Haemophilia B	9 (21.4)	1 (9.1)	4 (18.2)	4 (44.4)
Presence of inhibitors				
No	37 (88.1)	8 (72.7)	20 (90.9)	9 (100)
Yes	5 (11.9)	3 (27.3)	2 (9.1)	0
Disease severity				
Mild	8 (19.1)	1 (9.1)	4 (18.2)	3 (33.3)
Moderate	8 (19.1)	1 (9.1)	5 (22.7)	2 (22.2)
Severe	26 (61.8)	9 (81.8)	13 (59.1)	4 (44.5)
Treatment type				
On-demand therapy	12 (28.6)	1 (9.1)	7 (31.8)	4 (44.4)
Prophylaxis therapy	30 (71.4)	10 (91.9)	15 (68.2)	5 (55.6)
Types of concentrates[a]				
Plasma-derived factor concentrates	28 (66.7)	10 (91.9)	13 (59.1)	5 (55.6)
Bypassing agents	2 (4.8)	0	2 (9.1)	0
Frequency of infusion[a]				
1–2 times per week	18 (42.9)	6 (36.3)	7 (31.8)	5 (55.6)
3–4 times per week	8 (19.0)	2 (18.2)	6 (27.3)	0
≥5 times per week	4 (9.5)	2 (18.2)	2 (9.1)	0
Haemathrosis at target joint(s) in the previous year				
No	12 (28.5)	7 (63.6)	2 (9.1)	(33.3)
Yes	30 (71.5)	4 (36.4)	20 (90.9)	6 (66.7)
History of intracranial bleed				
No	33 (78.6)	9 (81.8)	18 (81.8)	7 (77.8)
Yes	9 (21.4)	2 (18.2)	4 (18.2)	3 (22.2)

(Continues)

TABLE 1 (Continued)

Sociodemographic variables	Total ($n = 42$) n (%)	Paediatrics (aged < 18 years) ($n = 11$)	Young adults (aged 18 to < 40 years) ($n = 22$)	Adults (aged > 40 years) ($n = 9$)
Other chronic conditions				
No	35 (80.9)	11 (100)	20 (90.1)	4 (44.4)
Yes	7 (19.0)	0	2 (9.1)	5 (55.6)
Hypertension	2 (4.8)		0	2 (22.2)
Diabetes	1 (2.4)		1 (4.5)	0
Hypercholesterolemia	1 (2.4)		0	1 (11.1)
Fatty liver disease	1 (2.4)		0	1 (11.1)
HBV or HCV or HIV carrier	5 (11.9)		1 (4.5)	4 (44.4)
Weight status[b]				
Normal weight	20 (47.6)	3 (27.2)	13 (59.1)	4 (44.4)
Overweight	12 (28.6)	4 (36.4)	4 (18.2)	4 (44.4)
Obese	10 (23.8)	4 (36.4)	5 (22.7)	1 (11.1)
Behavioural variables				
Non-Adherence[c] median [IQR]	58.0 [46.5–66.5]	47 [45–57]	61 [53–67]	65 [54–76.5]
Depression				
No/Mild	33 (78.6)	9 (81.8)	17 (77.3)	7 (77.8)
Moderate/Severe	9 (21.4)	2 (18.2)	5 (22.7)	2 (22.2)
Anxiety				
No/Mild	34 (81.0)	8 (72.7)	19 (86.4)	7 (77.8)
Moderate/Severe	8 (19.0)	3 (27.3)	3 (13.6)	2 (22.2)
Stress				
No/Mild	38 (90.5)	10 (90.9)	21 (95.5)	7 (77.8)
Moderate/Severe	4 (9.5)	1 (9.1)	1 (4.5)	2 (22.2)

Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency viruses; SD, standard deviation.
Boldface indicates statistical significance at $P \leq 0.05$.
[a]Only applicable to patients on prophylaxis treatment.
[b]Weight status for adult patients (≥18 years old) was defined using the Asian body mass index cutoffs: healthy weight (18.5–22.9 kg/m^2), overweight (23–24.9 kg/m^2) and obese (≥25 kg/m^2). Weight status for paediatric patients (<18 years old) was defined using age- and sex- adjusted percentiles from local growth charts: healthy weight (10 to <85th percentile), overweight (≥85th to <95th percentile), and obese (≥95th percentile).
[c]Patients on prophylactic treatment only. A higher score is indicative of worse adherence. Score ranged from 24 (most adherent) to 120 (least adherent).

the pre-identified clinical factors were diagnosis (haemophilia A vs. B), disease severity[5,27] (mild/moderate vs. severe), cerebral microbleeds[5] (yes vs. no), comorbidities[2,5] (yes vs. no), weight (normal vs. overweight/obese, as defined by Asian threshold of BMI ≤ 23.0 kg/m^2 and BMI > 23.0 kg/m^2, respectively), and bleeding events,[3,4,27,28] including hemarthrosis in the previous year (no vs. yes) and a history of intracranial bleeding (no vs. yes).[30,31] Behavioural factors included were adherence to therapy (for patients who were on prophylactic treatment) and mental health status (depression, anxiety, and stress).[28,32] Unstandardized point estimates (Est) and 95% confidence intervals (95% CI) were used to quantify the effect size for each association. A sensitivity analysis was conducted by repeating the multivariable analysis among patients without history of intracranial bleeding. All statistical analyses were performed using SAS (SAS 9.4, SAS Institute, Cary, NC) and were two-tailed. The significance threshold was set at $p < .05$.

3 | RESULTS

3.1 | Clinical characteristics

Fifty-one eligible patients were invited to take part in this study, of which six were unable to take part as they were overseas ($n = 3$) or were otherwise unavailable ($n = 3$). Three patients actively declined to take part. In total, 42 patients (response rate = 82.4%) provided consent and completed the study (Table 1).

The median participant age was 32.0 (interquartile range: 16.8–39.7) years, consisting 11 paediatric patients (median age 15.6 years), 22 young adult patients (median age 33.0 years), and 9 older adult patients (median age 55.2 years). Half of the employed adults ($n = 22$) had a monthly income of < HKD$20,000 (USD$2,565) ($n = 12/22$, 54.5%), which is close to or below the average median

monthly wage (~HKD 18,700) of an employed individual in Hong Kong.[33]

The majority of participants had haemophilia A (n = 33; 78.6%). Among the patients with moderate-to-severe disease severity (n = 34; 80.9%) and were indicated for prophylactic treatment, the majority (n = 30, 71.4%) received regular prophylactic treatment. The remaining patients (n = 12; 28.6%) received on-demand therapy only. Hemarthrosis in the previous year was common (n = 34; 80.9%). Nine patients had suffered from previous intracranial bleed (21.4%), all of whom had severe (n = 8) or moderate (n = 1) disease severity.

Nearly one-third of patients had additional comorbidities (n = 13; 30.9%). Five patients were carriers of hepatitis B (HBV), hepatitis C (HCV), or human immunodeficiency virus (HIV). Half of the patients were either overweight (n = 10; 23.8%) or obese (n = 11; 26.2%).

In terms of behavioural factors, up to one-fifth of patients reported either moderate/severe depression (n = 9; 21.4%), anxiety (n = 8; 19.0%), or stress (n = 4; 9.5%) symptoms during the study period. Among patients who were on prophylactic treatment, the median non-adherence score was low (58/120 points; IQR: 46.5–66.5), indicating high medication adherence among the patient cohort.

3.2 | Neurocognitive outcomes

After correcting for FDR, the haemophilia patients performed worse than the age-matched controls in terms of motor processing speed (p = .0009), visuomotor processing speed (p = .025), inattentiveness (p = .021), and cognitive flexibility (p = .0032) (Figure 1).

Significant (i.e. moderate to severe) impairments were most commonly seen in the domains of cognitive flexibility (n = 13; 30.9%), motor processing speed (n = 11; 26.2%), and visuomotor processing speed (n = 6; 14.3%) (Figure 2).

Among patients with a history of intracranial bleeding (n = 9), significant impairment in motor processing speed and cognitive flexibility was observed in four patients (44.4%), while the rates of impairment among patients without intracranial bleeding were 27.3% (n = 9/33) and 21.2% (n = 7/33), respectively (Supplement 2).

In terms of age group, the rates of significant impairment in cognitive flexibility were 18.2% (n = 2/11), 22.7% (n = 6/22), and 55.6% (n = 5/9) among paediatric patients, young adults, and older adults, respectively (Supplement 3).

3.3 | Neuroimaging outcomes

Six patients (14.3%) showed signs of cerebral microbleeds on MRI scans (Table 2). More than half of these individuals had haemophilia A (n = 4/6). Four patients had moderate (n = 1/6) or severe (n = 3/6) disease severity, and were receiving prophylactic treatment (n = 4/6), while the remaining two patients had mild disease severity and only received on-demand therapy. Four patients (66.6%) had a previous history of intracranial bleeding. One patient (16.7%) had developed

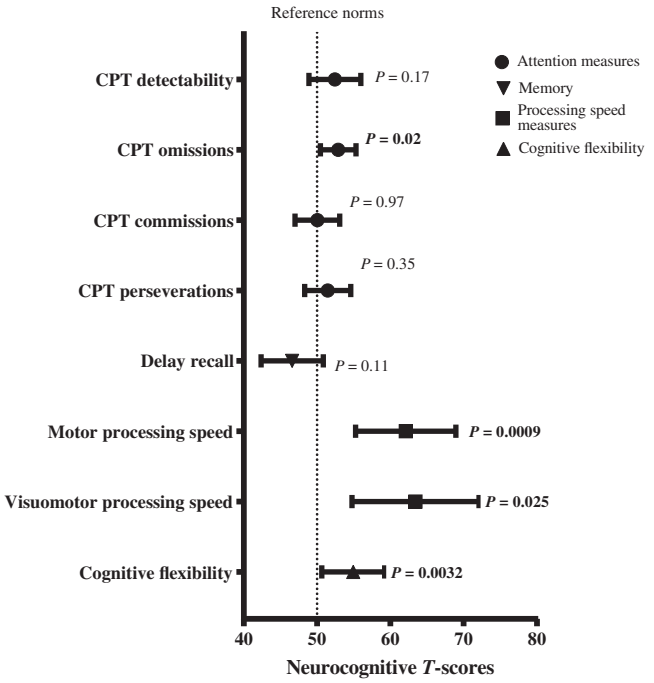

FIGURE 1 Neurocognitive outcomes as compared with reference norms caption: One-sample t-test was conducted to compare performances between patients and population norms (μ = 50), adjusting for false discovery rate. Only cognitive measures that differ from the age-adjusted reference norms at $P < .05$ were included in the multivariable analysis (Table 3).

autoantibodies against coagulation factor VIII. Three patients (50%; all > 50 years old) were carriers of either HBV, HCV, or HIV.

Most patients with evidence of cerebral microbleeds (n = 5/6) had microbleeds at more than one site. Microbleeds were largely confined to the lobar cortical grey matter and lobar subcortical and periventricular regions (n = 6/6). In terms of cognitive impairment, all patients (except Patient #6) had moderate-to-severe impairment in at least one cognitive domain.

Specifically, the youngest patient with cerebral microbleeds (Patient #1, < 18 years old) had a history of intracranial bleeding and frequent episodes of hemarthrosis. Although he was on prophylactic treatment, he had developed inhibitors to the clotting factor concentrates. He had severe impairments in cognitive flexibility and motor processing speed, and moderate memory impairment. Patient #5, who was an HIV carrier and diagnosed with clinical depression, had severe impairments across all cognitive domains.

3.4 | Factors associated with cognitive outcomes

After adjusting for age and education attainment, multivariable analysis (Table 3) revealed that patients with a history of hemarthrosis in the previous year had worse attention (Est = 7.62, 95% CI: 1.92–15.33 ; p = .049) and cognitive flexibility (Est = 8.64, 95% CI: 2.52–13.29; p = .043) than those with no such history. Haemophilia

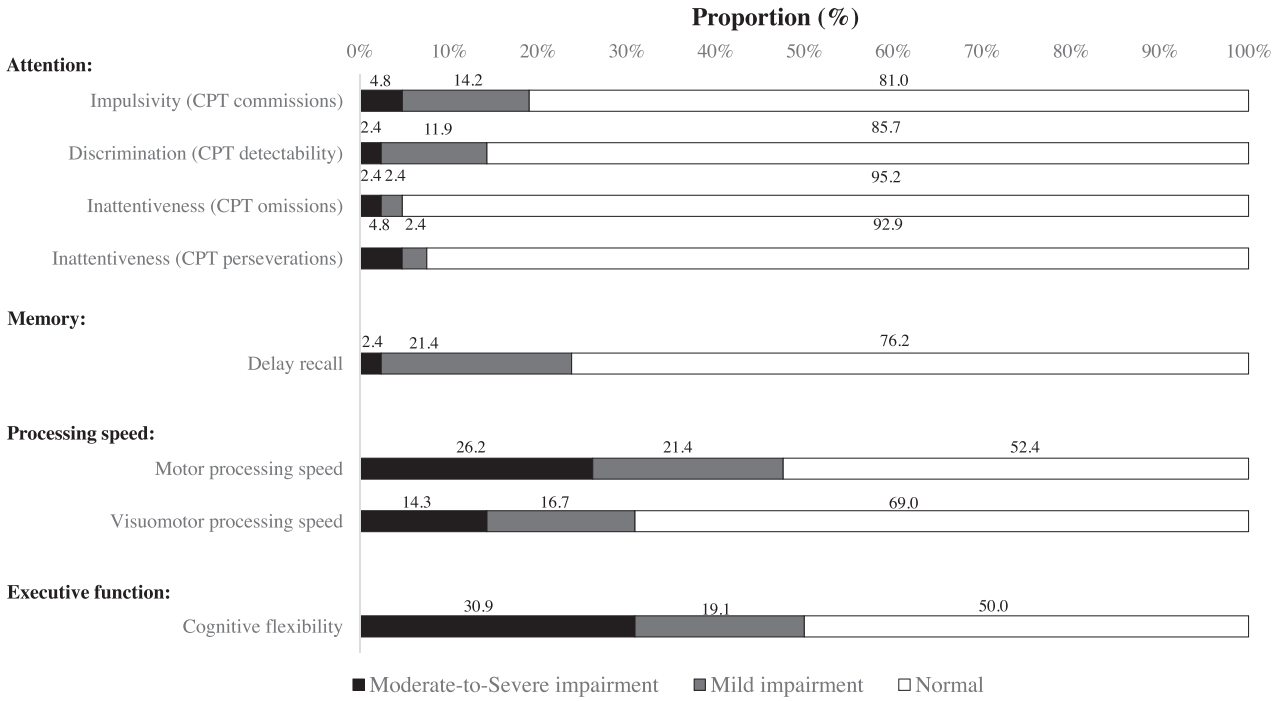

FIGURE 2 Rates of cognitive impairment caption: Impairment for each measure is defined as having a T-score ≥ 1.0 to 1.5 standard deviation (mild impairment) and T-score ≥ 1.5 standard deviation (moderate-to-severe impairment) of the age-adjusted published norms.

B patients demonstrated more inattentiveness than haemophilia A patients (Est = 12.09, 95% CI: 5.04–19.12; p = .0013). Compared to patients with a normal weight, patients who were overweight or obese had worse cognitive flexibility (Est = 6.23, 95% CI: 1.92–13.39; p = .026). Cognitive function was not significantly associated with disease severity, treatment type, or other comorbidities.

In terms of behavioural factors, depression (Est = 0.22, 95% CI: 0.10–0.55; p = .023) and anxiety (Est = 0.26, 95% CI: 0.19–0.41; p = .0069) were associated with inattentiveness. Anxiety severity was negatively correlated with cognitive flexibility performance (Est = 0.39, 95% CI: 0.16–1.66; p = .043). Among patients who were receiving prophylactic treatment, medication adherence was positively correlated with attention (Est = 0.30, 95% CI: 0.14–0.56; p = .024) and cognitive flexibility (Est = 0.28, 95% CI: 0.19–0.41; p = .037).

The results of the sensitivity analysis (Supplement 4) were similar to the main analysis. Among patients without history of intracranial bleeding, cognitive impairment was associated with hemarthrosis (p = .048), adherence (p = .049), depression (p = .048), anxiety (p = .025), though the effect sizes were attenuated due to a smaller sample size (Supplement 4).

4 | DISCUSSION

We found that a substantial proportion of patients with haemophilia in Hong Kong suffer from moderate-to-severe cognitive impairment in terms of processing speed and cognitive flexibility. Such impairments were more pronounced in patients who had experienced hemarthrosis in the previous year, suggesting that poorly managed haemophilia might be a potential risk factor. Psychological symptoms and medication adherence were also associated with cognitive outcomes. These findings could inform the development of patient-centred behavioural interventions with the goal of improving functional outcomes. Routine screening for psychosocial issues and cognitive deficits would enable timely behavioural interventions, such as special educational services and counselling support for younger patients. As cognitive function is a complex and multifactorial phenotype, the clinical and behavioural risk factors identified from this study should be validated in larger cohorts and interpreted in light of other interacting cultural, socio-environmental and lifestyle factors throughout the lifespan of patients with haemophilia.

Cerebral microbleeds were present in a minority (14.3%) of the study cohort, falling at the lower end of published prevalence estimates (7%–35%).[5,6] The relatively low rate of microbleeds might reflect the improved prophylactic treatment strategies and quality of care seen in the past decade. In Hong Kong, patients with haemophilia have regular consultations with their haematologists and a multidisciplinary team and clotting factor concentrates are fully subsidized by the government. We were unable to determine if the rate of microbleeds among those with haemophilia differs from that of the general population due to the absence of a healthy control group. However, the prevalence seen in our cohort (median age: 32 years old) was higher than the age-specific prevalence rate (6.5%) of the youngest cohort of healthy community dwelling adults (45—50 years old) of the landmark Rotterdam Scan Study.[34] Notably, this result has to be interpreted cautiously as the neuroimaging scan is only reflective of the patient's status at the study period and does the progression of the cerebral microbleeds. Studies in the general population has observed that age accounted for

TABLE 2 Characteristics of patients with cerebral bleeds on MRI ($n = 6$).

Patient number	1	2	3	4	5	6
Age (years)[a]	10–18	30–40	30–40	50–60	50–60	50–60
Haemophilia	A	A	A	A	B	B
Disease severity	Severe	Mild	Severe	Severe	Moderate	Mild
Treatment	Prophylaxis	On-demand	Prophylaxis	Prophylaxis	Prophylaxis	On-demand
Inhibitors	Yes	No	No	No	No	No
History of intracranial bleed	Yes	No	Yes	Yes	Yes	No
Haemathrosis (past year)	Yes	Yes	Yes	No	Yes	No
No. of haemathrosis episodes in the past 2 years	8	2	3	0	1	0
Other chronic conditions	–	–	Diabetes	HBV carrier, HIV	HIV, depression	Hypercholesterolemia, HBV carrier, fatty liver
Sites of bleed[b]						
Lobar cortical grey	Frontal (R) Parietal (L)	–	Temporal (R)	Parieto-occipital (L)	Occipital (L)	–
Lobar Subcortical	–	Frontoparietal (R)	Temporal (R) Occipital (R)	Parieto-occipital (L)	Occipital (L)	–
Periventricular	–	Lateral ventricle (L)	Posteior periventricular (R)	–	–	Posterior (R) Occipital horn (R)
Internal capsule	–	–	Posterior limb (R)	–	–	–
External capsule	–	–	External (R)	–	–	–
Cognitive impairment						
Attention	Normal	Normal	Normal	Severe	Severe	Normal
Immediate recall	Moderate	Normal	Normal	Moderate	Severe	Normal
Delay recall	Moderate	Normal	Normal	Moderate	Severe	Normal
Motor processing speed	Severe	Normal	Severe	Severe	Severe	Normal
Visuomotor processing speed	Normal	Normal	Normal	Normal	Severe	Normal
Cognitive flexibility	Severe	Moderate	Moderate	Normal	Severe	Normal

[a]The age range, instead of the exact age in years, was presented. This measure is taken to minimize identifiable data and to protect patient privacy.
[b]None of the patients presented with cerebral bleeds at the basal ganglia, thalami, corpus callosum, brainstem and cerebellum.

TABLE 3 Factors associated with cognitive outcomes.

	Inattentiveness[a,b]			Motor processing speed[a,b]			Visuomotor processing speed[a,b]			Cognitive flexibility[a,b]		
	Est	95% CI	*P*	Est	95% CI	*P*	Est	95% CI	*P*	Est	95% CI	*P*
Base model												
Age	−0.043	−0.21–0.24	.96	0.11	−0.34–0.58	.60	−0.083	−0.37–0.20	.56	−0.20	−0.77–0.36	.47
Education attainment												
Post-secondary school or above	Ref			Ref			Ref			Ref		
Secondary school or below	2.56	−3.67–8.79	.41	5.79	−8.13–19.7	.40	5.14	−3.49–13.7	.23	15.21	−1.78–32.21	.078
Clinical variables												
Diagnosis[b]												
Haemophilia A	Ref			Ref			Ref			Ref		
Haemophilia B	12.09	5.04–19.12	**.0013**	3.94	−14.0–21.98	.66	2.45	−8.72–13.64	.65	5.73	−16.25–27.72	.60
Severity												
Mild	Ref			Ref			Ref			Ref		
Moderate/Severe	3.63	−4.52–11.79	.90	7.24	−17.70–19.15	.93	4.26	−7.08–15.60	.45	21.25	−0.12–42.6	.051
Hemarthrosis (previous year)												
No	Ref			Ref			Ref			Ref		
Yes	7.62	1.92–15.33	**.049**	10.71	−7.07–28.50	.23	2.12	−9.09–13.34	.70	8.64	2.52–13.29	**.043**
Intracranial bleed												
No	Ref			Ref			Ref			Ref		
Yes	2.71	−4.91–10.34	.47	9.82	−7.04–26.70	.24	−0.72	−11.37–9.92	.89	−1.26	−22.22–19.69	.90
Other comorbidities												
No	Ref			Ref			Ref			Ref		
Yes	2.02	−5.29–9.33	.57	4.55	−11.79–20.90	.57	3.78	−6.31–13.88	.45	12.36	−7.24–31.98	.20
Weight status												
Normal weight	Ref			Ref			Ref			Ref		
Overweight/obese	2.68	−3.59–8.95	.39	0.68	−13.47–14.84	.92	2.43	−6.30–11.18	.57	6.23	1.92–13.39	**.026**
Behavioural variables												
Adherence[a,c]	.30	0.14–0.56	**.024**	0.04	−0.41–0.50	.84	0.14	−0.19–0.48	.39	0.28	0.19–0.41	**.037**
Depression[a]	.22	0.10–0.55	**.023**	0.23	−0.74–1.20	.63	0.13	−0.47–0.73	.65	0.01	−1.17–1.20	.98
Anxiety[a]	.26	0.19–0.41	**.0069**	0.13	−0.90–1.17	.79	0.25	−0.38–0.89	.42	0.39	0.16–1.66	**.043**
Stress[a]	.054	−0.35–0.46	.78	0.02	−0.88–0.93	.95	0.08	−0.47–0.65	.74	0.30	−0.80–1.40	.58

Note: The risk factors, cerebral bleeds ($n = 6$) and presence of inhibitors ($n = 5$), were excluded from the multivariable analysis due to the small sample size.
Abbreviations: CPT, conners performance Test-III for attention; Est, estimate; Ref, reference group; SE, standard error.
[a]A higher value was indicative of worse functioning.
[b]Association between each clinical or behaviour variable and neurocognitive outcome was tested using general linear models, adjusted for age and education attainment. Only cognitive measures that differ from the age-adjusted reference norms at $P < .05$ (Figure 1) were included in the multivariable analysis.
[c]Among users of prophylactic treatment only. A higher score is indicative of poorer adherence.

1 to 10% cumulative risk for cerebral microbleed occurrence over time, and the development of comorbidities could increase the progressive risk to 25%.[35] Our future work includes a prospective follow-up with multiple measurement to delineate changes in the microbleed count and size, and to correlate it with the trajectories of cognitive outcomes in these patients over the lifespan.

A quarter of the study cohort had a previous history of intracranial bleeding, which is a known risk factor for cerebral microbleed and cognitive impairment. Four out of the 6 patients with microbleed have had an intracranial bleeding event. Although our sample size was too small to identify specific risk factors for microbleeds, the descriptive characteristics of individuals with microbleeds were consistent with those reported in the literature: three or more of the six individuals with microbleeds had moderate-to-severe disease severity,[5,27] comorbidities,[2,5] and a previous history of intracranial bleeds.[27,28] To highlight, the three patients who were older than 50 years old were carriers of HBV or HIV, which is associated with chronic inflammation causing vulnerabilities to the brain microstructure, and is a known risk factor for cerebral microbleeds in patients with haemophilia.[36,37] Fortunately, the risk of viral infection in younger patients is almost negligible now with the use of purified plasma-derived factor concentrates. Most microbleeds were seen in the frontal and parietal regions, which aligns with the executive dysfunction and somatosensory processing impairments observed in these individuals.

Out of the six patients who had developed cerebral microbleeds on neuroimaging, we found that two patients (33.3%) had mild disease severity and no previous documented history of intracranial bleeds. One study has reported that the rate of intracranial haemorrhage was 45.2% among adults with mild haemophilia, with uncontrolled hypertension as a potential risk factor.[38] Patients with mild haemophilia may have few symptoms and little need of healthcare services, hence the related complications are often under-diagnosed and tend to be neglected by the patient.[39] It is possible that these patients might have experienced a subclinical trauma that did not result in significant symptoms, and such small-vessel haemorrhage might remain undetected in a typical clinical setting, though fortunately, these two individuals' cognitive performance was normal on all most/all domains. To note, we do not expect any cerebral microbleed to be present in healthy children without organic neurological disorders,[40] yet, cerebral microbleed was detected in one paediatric patient who was on prophylactic treatment but had developed inhibitors. Patients presenting with specific risk factors must therefore be monitored regularly for signs of cerebral bleeds, as cerebral microbleeds could measurably impact their functional outcomes.

With reference to age-adjusted population norms, we found that one-third of haemophilia patients have moderate-to-severe impairment of higher-order cognitive function, including cognitive flexibility and visuomotor and motor processing speed. In the absence of a healthy age-matched control group for comparison, our study could not demonstrate that the rates of impairment is different between patients with haemophilia and healthy controls. However, several recent studies have reported cognitive impairments in patients with haemophilia, although there have been inconsistencies among the risk factors identified.[4,5,27,28] For example, there is substantial evidence from the literature that observed acute cognitive deficits in individuals who suffered from intracranial haemorrhage, as well as progressive cognitive deterioration that is driven by the accumulation of diffuse vascular and non-vascular pathology.[30,31] Intracranial bleeding is a known risk factor of cognitive impairment in patients with haemophilia, and one study even found that the total number of bleeding events was independently associated with decreased cognitive function in patients with haemophilia.[27] Our multivariable analysis did not identify intracranial haemorrhage as a significant predictor of impairment. However, the rates of motor processing speed impairment and cognitive flexibility are seemingly higher in the minority of patients with a history of intracranial bleeding (Supplement 2), as compared to those who did not. The exact pathophysiological mechanisms underlying such cognitive impairments are also not well established. One study proposed that structural alterations in the brain and degeneration of white and grey matter, especially the frontal lobe, could lead to such deficits in higher-order functioning.[9] These microstructural changes could explain why patients still suffer from cognitive impairment in the absence of cerebral microbleeds on MRI or a history of intracranial haemorrhages. This speculation is further supported by our finding that patients with a history of hemarthrosis in the past year had worse attention and cognitive flexibility function than those who did not, suggesting poorly managed haemophilia as a potential risk factor. This finding should be interpreted cautiously as we did not examine the severity and number of bleeding episodes; future work should further delineate the impact of the frequency, sites, and nature/severity of hemarthrosis episodes on functional outcomes. As haemophilia is an early onset and chronic disorder, compared to acute conditions such as stroke or brain trauma, patients have likely developed adaptive or compensatory strategies. Future studies should evaluate the impact of cognitive impairment on functional capacity (educational/vocational attainment and occupational function) and health-related quality of life in patients with haemophilia.

In addition to clinical risk factors, studies have also proposed that biopsychosocial factors can contribute to cognitive impairment in patients with haemophilia.[28] Depression and anxiety are more common among this population than the general population, likely because patients have to manage complex medication regimens, infusion and joint pain, and frequent visits to healthcare services.[10,11,41,42] Although we did not conduct clinical evaluations of mental health disorders in our cohort, our validated screening tool (DASS-21) showed that one-fifth of patients reported moderate-to-severe depressive or/and anxiety symptoms. We have also previously reported that adult patients with haemophilia in Hong Kong reported poorer quality of life, particularly in the domains of self-perception, feelings, and perception of the future.[26] Furthermore, this study was conducted during the Coronavirus pandemic; increases in psychological distress were reported during that period in the local population.[43] Our results suggest that depression and anxiety are associated with impaired attention and cognitive flexibility. Neuropsychological impairment has also been reported, most notably in executive dysfunction, among individuals with clinical psychiatric disorders.[44,45] Our results

collectively underscore the importance of developing holistic strategies to address patients' health and psychosocial needs. Schools and non-governmental organizations should collaborate closely to identify paediatric and young adult patients displaying early signs of behavioural issues; these individuals should undergo regular neuropsychological screening and be monitored closely for cognitive deficits that could impact their academic and social performance.

We also found that adherence, another behavioural construct, is associated with cognitive impairment. Non-adherence itself is a complex behavioural concept, and its association with cognitive function might result from worse self-management of the condition, lower health literacy and socioeconomic status.[32] We have previously reported that poor adherence is correlated with poor self-perception of health and future outlook among patients with haemophilia in Hong Kong.[26] Similarly, our finding in this study that overweight/obese patients have decreased cognitive flexibility might be explained by the association between lifestyle behaviour and cognitive outcomes.[46] Future work should include a prospective and objective assessment of treatment adherence and lifestyle behaviours among patients with haemophilia, and its impact on functional outcomes.

The strength of this study lies in the use of comprehensive neurocognitive tests to assess cognitive performance, and the subsequent correlation of the data with clinical characteristics and neuroimaging. However, this study has a few limitations. First, the sample size was relatively smaller than those of other previous studies. However, the high response rate and broad sampling frame from the three public hospitals and through a patient organization ensure a reasonable degree of generalizability to other patients in Hong Kong, and even those in urban/city areas of mainland China. We did not include a control group of subjects without haemophilia for comparison. We faced challenges with recruiting generalizable group of community age-matched controls as our study population consisted of patients with a wide age range. Furthermore, the study period was during the Coronavirus pandemic when restrictions were imposed to minimize members of the public from visiting the public hospitals (i.e. the study sites) without any medical indications. However, the rates of impairment presented in this study were based on reference norms (in particular, Chinese norms for measures of visuomotor processing speed and cognitive flexibility). These neuropsychological tests and published norms (Supplement 1) are also adopted by local neuropsychologists and cognitive studies in other diseased populations.[47,48] Our findings should be validated prospectively in larger haemophilia cohorts and compared with an age- and matched control group. Second, this is a cross-sectional study, and most patients did not undergo any prior neuroimaging unless clinically indicated. Hence, we could not establish a temporal relationship among the clinical factors, neuroimaging, and cognitive outcomes. For example, even though hemosiderin deposits are suggestive of previous occurrences of bleeding, most patients did not have prior scans for comparison. We were also not able to ascertain if patients with normal brain scans had simply recovered from previous injuries. The MRI technique used in this study is the high resolution sequences which are sensitive for clinical detection of any structural brain abnormalities such as hemosiderin, ischemic insults and white matter changes. However, these sequences are good for macroscopic structural changes and might not be sensitive enough to identify local microstructural tissue damage. Future work should include more sophisticated functional neuroimaging techniques, such as diffusion tensor imaging, to enable in vivo assessment of the spatial and temporal patterns of microstructural changes. Lastly, this study used standard neurocognitive tests. However, the interpretation of the neurocognitive findings should take into consideration the nature of the patients' health conditions. For example, the high rate of visuomotor and motor processing speed impairments, particularly in the older adult patients, might have resulted from distal interphalangeal joint stiffness and age-related arthropathy, rather than impaired somatosensory function.

5 | CONCLUSION

A substantial proportion of patients with haemophilia demonstrated moderate-to-severe cognitive impairment, particularly in terms of higher-order thinking skills, such as processing speed and executive function. Recent episodes of hemarthrosis and greater psychological symptom burden were associated with such impairment. Encouragingly, the rate of cerebral microbleeds was low. However, high-risk patients with multiple comorbidities, a previous history of intracranial haemorrhage, and poorly controlled haemophilia should be monitored for early signs of cerebral bleeding. Compensatory interventions, including behavioural and cognitive strategies, should be incorporated into routine care to accommodate cognitive deficits.

AUTHOR CONTRIBUTIONS

Study conception and design: All authors Data collection: Yin Ting Cheung, Chung Tin Ma, Henry Hon Wai Lam, Siu Cheung Ling, Kevin Kwok, Chak Ho Li, Chung Yin Ha, Sze Fai Yip, Raymond Siu Ming Wong, Chi Kong Li. Analysis and interpretation of results: Yin Ting Cheung, Winnie Chiu Wing Chu Draft manuscript preparation: Yin Ting Cheung All authors reviewed the results and approved the final version of the manuscript

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CONFLICT OF INTEREST STATEMENT

The authors have no competing interests, All authors have no conflict of interest to disclose.

ETHICS STATEMENT

This study was approved by The Chinese University of Hong Kong and New Territories East Cluster (Ref: 2019–023).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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REFERENCES

1. Hegde A, Nair R, Upadhyaya S. Spontaneous intracerebral hemorrhage in hemophiliacs—a treatment dilemma. *Int J Surg Case Rep*. 2016;29:17-19. doi:10.1016/j.ijscr.2016.10.046
2. De Cristofaro R, Franchini M. Intracranial haemorrhage in children and adults with haemophilia A and B: a literature review of the last 20 years. *Blood Transfus*. 2019;17(5):334-335. doi:10.2450/2019.0036-19 2019/09//
3. Morales G, Matute E, O'Callaghan ET, Murray J, Tlacuilo-Parra A. Visuoperceptual sequelae in children with hemophilia and intracranial hemorrhage. *Transl Pediatr*. 2015;4(1):45-56. doi:10.3978/j.issn.2224-4336.2014.12.01
4. Miles BS, Anderson P, Agostino A, et al. Effect of intracranial bleeds on the neurocognitive, academic, behavioural and adaptive functioning of boys with haemophilia. *Haemophilia*. 2012;18(2):229-234. doi:10.1111/j.1365-2516.2011.02632.x
5. Zanon E, Manara R, Milan M, et al. Cognitive dysfunctions and cerebral microbleeds in adult patients with haemophilia A: a clinical and MRI pilot-study. *Thromb Res*. 2014;134(4):851-855. doi:10.1016/j.thromres.2014.08.005
6. Husseinzadeh H, Chiasakul T, Gimotty PA, et al. Prevalence of and risk factors for cerebral microbleeds among adult patients with haemophilia A or B. *Haemophilia*. 2018;24(2):271-277. doi:10.1111/hae.13398
7. Greenberg SM, Vernooij MW, Cordonnier C, et al. Cerebral microbleeds: a guide to detection and interpretation. *Lancet Neurol*. 2009;8(2):165-174. doi:10.1016/s1474-4422(09)70013-4
8. Humphries TJ, Mathew P. Cerebral microbleeds: hearing through the silence-a narrative review. *Curr Med Res Opin*. 2019;35(2):359-366. doi:10.1080/03007995.2018.1521787
9. Hu D, Kang H, Lv Y, et al. Preliminary evaluation of altered brain microstructure in the emotion–cognition region in children with haemophilia A: a diffusional kurtosis imaging study. *Haemophilia*. 2017;23(2):e99-e104. doi:10.1111/hae.13159
10. Steen Carlsson K, Winding B, Astermark J, et al. Pain, depression and anxiety in people with haemophilia from three Nordic countries: cross-sectional survey data from the MIND study. *Haemophilia*. 2022;28(4):557-567. doi:10.1111/hae.14571
11. Jiménez-Cebrián AM, Palomo-López P, Becerro-de-Bengoa Vallejo R, et al. Impact of depression on patients with hemophilia: a retrospective case-control research. *Front Psychiatry*. 2022;13:892321. doi:10.3389/fpsyt.2022.892321
12. Au WY, Lee V, Kho B, et al. A synopsis of current haemophilia care in Hong Kong. *Hong Kong Med J*. 2011;17(3):189.
13. South China Morning Post "'No centralised system' for haemophilia patients" Published April 17, 2016. Accessed on October 8. URL: https://www.scmp.com/news/hong-kong/health-environment/article/1936708/no-centralised-system-haemophilia-patients , 2021.
14. Conners CK, Sitarenios G. Conners' continuous performance test (CPT). *Encyclopedia of Clinical Neuropsychology*. 2011:681-683. doi:10.1007/978-0-387-79948-3_1535 (Book, Section)
15. Casarotti A, Papagno C, Zarino B. Modified Taylor Complex Figure: normative data from 290 adults. *J Neuropsychol*. 2014;8(2):186-198. doi:10.1111/jnp.12019
16. Strauss E, Sherman EMS, Spreen O. *Aœ compendium of neuropsychological tests*. Oxford Univ. Press; 2006. 3.
17. Lee T, Yuen K, Chan C. Normative data for neuropsychological measures of fluency, attention, and memory measures for Hong Kong Chinese. *J Clin Exp Neuropsychol*. 2002;24(5):615-632. doi:10.1076/jcen.24.5.615.1001
18. Shi C, Kang L, Yao S, et al. The MATRICS Consensus Cognitive Battery (MCCB): co-norming and standardization in China. *Schizophr Res*. 2015;169(1-3):109-115. doi:10.1016/j.schres.2015.09.003
19. Viswanathan A, Chabriat H. Cerebral microhemorrhage. *Stroke*. 2006;37(2):550-555. doi:10.1161/01.Str.0000199847.96188.12
20. Akoudad S, Wolters FJ, Viswanathan A, et al. Association of cerebral microbleeds with cognitive decline and dementia. *JAMA Neurol*. 2016;73(8):934-943. doi:10.1001/jamaneurol.2016.1017
21. Martinez-Ramirez S, Greenberg SM, Viswanathan A. Cerebral microbleeds: overview and implications in cognitive impairment. *Alzheimers Res Ther*. 2014;6(3):33. doi:10.1186/alzrt263 2014/06/11
22. van Norden AG, van den Berg HA, de Laat KF, Gons RA, van Dijk EJ, de Leeuw FE. Frontal and temporal microbleeds are related to cognitive function: the Radboud University Nijmegen Diffusion Tensor and Magnetic Resonance Cohort (RUN DMC) Study. *Stroke*. 2011;42(12):3382-3386. doi:10.1161/strokeaha.111.629634
23. Osman A, Wong JL, Bagge CL, Freedenthal S, Gutierrez PM, Lozano G. The depression anxiety stress scales—21 (DASS-21): further examination of dimensions, scale reliability, and correlates. *J Clin Psychol*. 2012;68(12):1322-1338. doi:10.1002/jclp.21908
24. Wang K, Shi HS, Geng FL, et al. Cross-cultural validation of the depression anxiety stress scale-21 in China. *Psychol Assess*. 2016;28(5):e88-e100. doi:10.1037/pas0000207
25. Duncan N, Kronenberger W, Roberson C, Shapiro A. VERITAS-Pro: a new measure of adherence to prophylactic regimens in haemophilia. *Haemophilia*. 2010;16(2):247-255. doi:10.1111/j.1365-2516.2009.02129.x
26. Cheung YT, Lam PH, Lam HHW, et al. Treatment adherence and health-related quality of life in patients with hemophilia in Hong Kong. *Int J Environ Res Public Health*. 2022;19(11). doi:10.3390/ijerph19116496
27. Buranahirun C, Walsh KS, Mrakotsky C, et al. Neuropsychological function in children with hemophilia: a review of the Hemophilia Growth and Development Study and introduction of the current eTHINK study. *Pediatr Blood Cancer*. 2020;67(1):e28004. doi:10.1002/pbc.28004
28. Cognitiv Firoozi. Emotional, and behavioral problems of children with hemophilia. research. *Iran J Blood Cancer*. 2017;9(3):69-74.
29. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J R Stat Soc Ser B Methodol*. 1995;57(1):289-300.
30. Potter T, Lioutas VA, Tano M, et al. Cognitive impairment after intracerebral hemorrhage: a systematic review of current evidence and knowledge gaps. *Front Neurol*. 2021;12:716632. doi:10.3389/fneur.2021.716632
31. Xiong L, Reijmer YD, Charidimou A, Cordonnier C, Viswanathan A. Intracerebral hemorrhage and cognitive impairment. *Biochim Biophys Acta - Mol Basis Dis*. 2016;1862(5):939-944. doi:10.1016/j.bbadis.2015.12.011
32. Thornburg CD, Duncan NA. Treatment adherence in hemophilia. *Patient Prefer Adherence*. 2017;11:1677-1686. doi:10.2147/PPA.S139851
33. Census and Statistics Department, *The Government of the Hong Kong Special Administrative Region. Wages and Labour Earnings*. Accessed on December 30, URL: https://www.censtatd.gov.hk/en/scode210.html 2022.
34. Poels MM, Vernooij MW, Ikram MA, et al. Prevalence and risk factors of cerebral microbleeds: an update of the Rotterdam scan study. *Stroke*. 2010;41(10):S103-6. doi:10.1161/strokeaha.110.595181 Suppl

35. Daugherty AM, Raz N. Incident risk and progression of cerebral microbleeds in healthy adults: a multi-occasion longitudinal study. *Neurobiol Aging*. 2017;59:22-29. doi:10.1016/j.neurobiolaging.2017.07.003
36. Cho JY, Lee WS, Park YS, Lee SH, Koh JS. Clinical characteristics and prognostic factors in hemophiliacs with intracranial hemorrhage: a single-center, retrospective experience. *Indian J Hematol Blood Transfus*. 2016;32(4):488-493. doi:10.1007/s12288-016-0637-3
37. Endo T, Goto H, Miyashita N, et al. The prevalence of cerebral microbleeds in HIV-infected hemophilia patients. *J AIDS Clin Res*. 2017;8. doi:10.4172/2155-6113.1000747
38. Zanon E, Pasca S, Demartis F, et al. Intracranial haemorrhage in haemophilia patients is still an open issue: the final results of the Italian EMO.REC Registry. *J Clin Med*. 2022;11(7). doi:10.3390/jcm11071969
39. Benson G, Auerswald G, Dolan G, et al. Diagnosis and care of patients with mild haemophilia: practical recommendations for clinical management. *Blood Transfus*. 2018;16(6):535-544. doi:10.2450/2017.0150-17
40. Dangouloff-Ros V, Roux CJ, Boulouis G, et al. Incidental brain MRI findings in children: a systematic review and meta-analysis. *AJNR Am J Neuroradiol*. 2019;40(11):1818-1823. doi:10.3174/ajnr.A6281
41. Sun J, Zhao Y, Yang R, Guan T, Iorio A. The demographics, treatment characteristics and quality of life of adult people with haemophilia in China - results from the HERO study. *Haemophilia*. 2017;23(1):89-97. doi:10.1111/hae.13071
42. Al-Huniti A, Reyes Hernandez M, Ten Eyck P, Staber JM. Mental health disorders in haemophilia: systematic literature review and meta-analysis. *Haemophilia*. 2020;26(3):431-442. doi:10.1111/hae.13960
43. Zhao SZ, Wong JYH, Luk TT, Wai AKC, Lam TH, Wang MP. Mental health crisis under COVID-19 pandemic in Hong Kong, China. *Int J Infect Dis*. 2020;100:431-433. doi:10.1016/j.ijid.2020.09.030 2020/11/01/
44. Testa R, Pantelis C. The role of executive functions in psychiatric disorders. In: Pantelis C, Allen NB, Wood SJ, eds. *The neuropsychology of mental illness*. Cambridge University Press; 2009:117-137.
45. Warren SL, Heller W, Miller GA. The structure of executive dysfunction in depression and anxiety. *J Affect Disord*. 2021;279:208-216. doi:10.1016/j.jad.2020.09.132
46. Cadar D, Pikhart H, Mishra G, Stephen A, Kuh D, Richards M. The role of lifestyle behaviors on 20-year cognitive decline. *J Aging Res*. 2012;2012:304014. doi:10.1155/2012/304014
47. Peng L, Yang LS, Yam P, et al. Neurocognitive and behavioral outcomes of chinese survivors of childhood lymphoblastic leukemia. *Front Oncol*. 2021;11:655669. doi:10.3389/fonc.2021.655669
48. Cheung YT, Ma CT, Li MCH, et al. Associations between lifestyle factors and neurocognitive impairment among chinese adolescent and young adult (AYA) survivors of sarcoma. *Cancers (Basel)*. 2023;15(3):799.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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