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CONTENTS

Editorial

- **Meguro Parasitological Museum – A Wonderful Experience Full of Surprises** 1
Kamruddin Ahmed and Siat Yee Fong

Original Articles

- **Exploring the Awareness, Perception, Acceptability and Confidence Level Towards Telerehabilitation among Stroke Patients' Caregivers in the Federal Territory of Malaysia** 5
Nik Nasihah Nik Ramli, Amirul Fikri Khamarul Bahrain, Ayu Puspita Sari Ainulhakim, Darmini Selvan
- **Health-Related Quality of Life (HRQoL) and Its Associated Factors Among Post-COVID-19 Patients at Three Months in a Tertiary Hospital of Bangladesh** 15
Nisat Zabin, Asfaq Rafeed Rahman, Sadia Amin, AKM Mosharraf Hossain, Shamim Ahmed, Nayma Sultana, Rifat Chowdhury

Review Article

- **Escape from Original Home: Do Metastatic Cells Stay Dormant or Destructive?** 26
Aye Aye Wynn, Nang Khin Mya, Tin Tin Thein

Short Communication

- **Postgraduate Nursing Education in Malaysia and Advanced Nursing Practice: Where Are We and What's Next?** 38
Noor Azizah Mohd Ali, Khin Thandar Aung, Hanida Hani Mohd Mokhtar, Ashikin Atan, Hairanni Mohd Noh, Sarina Ahmad

Case Reports

- **An Uncommon Aetiology of Native Valve Infective Endocarditis: *Corynebacterium glutamicum* Infective Endocarditis** 43
Carwen Siaw, Nor Izzah Binti Mazan, Seng Wee Cheo, Qin Jian Low
- **Helminth Infestation Causing Anaemia in Pregnancy Attending Primary Care Clinic: A Case Report** 50
Yashdev Atri Roop Kishore, Mohd Shaiful Ehsan Shalihin

ORIGINAL ARTICLE

Exploring the Awareness, Perception, Acceptability and Confidence Level Towards Telerehabilitation among Stroke Patients' Caregivers in the Federal Territory of Malaysia

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ABSTRACT

Telerehabilitation is the ability to provide distance support, evaluation and intervention to individuals who are undergoing rehabilitation therapy through telecommunication. This study aimed to explore the awareness, acceptability and confidence level towards telerehabilitation among caregivers of cerebral stroke patients in the federal territory of Malaysia. A cross-sectional study was conducted amongst stroke patients' caregivers from general hospitals in the federal territory of Malaysia. Descriptive statistics were used to analyse the awareness, acceptability and confidence level towards telerehabilitation technology among stroke patients' caregivers. The correlation between confidence level in using technology devices and their acceptance level of telerehabilitation was assessed by using Spearman correlation analysis. Results showed that 70% of caregivers were aware of the telerehabilitation technology, amongst which 60.5% were willing to use the technology for rehabilitation purposes. Out of all the types of devices, 50% of caregivers demonstrated a high confidence level in using smartphones. However, only 25.7% demonstrated a high confidence level in using video call services for telerehabilitation service. In conclusion, the majority of caregivers in the federal territory of Malaysia demonstrated a positive attitude towards telerehabilitation services for stroke patients.

INTRODUCTION

Stroke is defined as a neurological deficit due to interruption of blood supply to the brain which lasts for more than 24 h (Alrabghi et al., 2018). Stroke can be classified into two categories based on aetiology, which are ischaemic stroke and haemorrhagic stroke. In ischaemic stroke, a neurological deficit occurs due to blockage of blood supply to the brain. This blockage can be caused by atherosclerotic (50%), embolic (25%) or lacunar stroke (25%) (Wittenauer, 2013). Approximately 87% of total stroke cases were recorded as ischaemic stroke (Alrabghi et al., 2018). Haemorrhagic stroke occurs primarily due to sudden rupture of blood vessels in the brain, which accounts for 13% of total stroke cases (Alrabghi et al., 2018). For ischaemic stroke, blood flow to the brain must be immediately restored to minimise the injury. This is done by using a recombinant tissue plasminogen activator (rt-PA) that breaks up the blood clot and allows blood circulation in the brain (Hadley et al., 2020). On the other hand, haemorrhagic stroke treatment aims to regulate bleeding and reduce pressure in the brain via surgical intervention. As there is no cure for stroke since the brain tissue injury is permanent; hence, stroke management is more focused on neurological deficit improvement via rehabilitation therapy (Hadley et al., 2020).

Rehabilitation therapy is a set of interventions to enhance individual functioning and reduce disability that has occurred due to stroke. It enables individuals to be sufficiently independent in daily activities and improve their quality of life (McGlinchey et al., 2018). Rehabilitation can be categorised into three main categories which comprise occupational therapy, physical therapy and speech therapy. Generally, occupational therapy aims to improve the patient's ability to complete tasks so that he can participate in self-care practices, work and everyday tasks. On the other hand, physical therapy focuses on improving the patient's gait, muscle functions and pain management (Beaulieu et al., 2015). Next, speech therapy

helps in treating speech issues, for example, communication, vocalisation and swallowing problems (Beaulieu et al., 2015). In Malaysia, implementing constructive rehabilitation therapy needs a collective effort from the stroke unit, which is a team of specially trained staff responsible for coordinating multidisciplinary care for stroke patients (Abdul Aziz et al., 2014). They include neurologists, geriatricians or general physicians with an interest in stroke, rehabilitation physicians, pharmacists, rehabilitation nurses, physiotherapists, occupational therapists and speech therapists (Abdul Aziz et al., 2014). Stroke patients will have access to the stroke unit to monitor their health. Then, rehabilitation will be initiated based on the patient's disability to improve their physical functions (Abdul Aziz et al., 2014).

Telerehabilitation is the ability to provide distance support, evaluation and intervention to individuals who are undergoing rehabilitation therapy through telecommunication services (Laver et al., 2020). It is one of the interventions that offer distance support and is beneficial to both patients and their caregivers. Moreover, it is implemented for stroke recovery worldwide (Laver et al., 2020). A wide range of telerehabilitation programmes such as robot-assisted therapy, virtual reality therapy, games and home-based telerehabilitation programmes are used by stroke patients. These telerehabilitation programmes were the results of innovative development to ensure that patients receive sufficient therapeutic care, especially in the early stage of stroke when complications are more common (Chen et al., 2019). Various technologies are used as mediums for telerehabilitation, such as robotic devices, tablets, virtual reality, games, 3D monitoring, audio-visual, electrical stimulation, static bicycles, video conference, and mobile phones (Appleby et al., 2019; Chen et al., 2019; Nik Ramli et al., 2021; Schröder et al., 2019; Wahyuni et al., 2020). Published studies have demonstrated the effectiveness of using hand-held tablets, personal computers, laptops

and mobile phones as the telerehabilitation mediums and these interventions were reported to be as effective as conventional outpatient rehabilitation for improving functional recovery in stroke patients, and thus they could ease the caregivers' burden (Laver et al., 2020). A recent study concluded that home-based rehabilitation had minimised hospitalisation time, and improved family bonding and the stroke patients' quality of life (Mahmood et al., 2019). Consecutively, this significantly lowers depression levels and anxiety among patients as well as caregivers as compared to hospital-based rehabilitation (Mahmood et al., 2019). Despite these achievements of telerehabilitation, studies to clarify the perspectives of Malaysian stroke patients' caregivers on telerehabilitation are lacking. This study primarily intends to explore their awareness, acceptability and confidence level of telerehabilitation amongst stroke patients' caregivers in the federal territory of Malaysia. Furthermore, their perception of telerehabilitation to review its practicality to the reality of Malaysian stroke patients and their caregivers was explored.

MATERIALS AND METHODS

Study Design and Participants

This was a cross-sectional questionnaire-based study which was conducted among stroke patients' caregivers. Purposive sampling was applied and participants were stroke patients' caregivers at the rehabilitation department of Cheras Rehabilitation Hospital, Putrajaya Hospital and Kuala Lumpur Hospital. Participants were eligible if they were above 18 years old, and able to read, write and comprehend text in English or Bahasa Melayu. The participants were directed to a one-time online survey, whereby they could choose either the English or Bahasa Melayu version via a link or QR code. The information sheet and informed consent form were uploaded on the first page of the survey link. Ethical

approval for this study was obtained from the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia (IEC: IEC: KKM/NIHSEC/P20-2598).

Sample Size

The sample size was calculated by using the Kish sample size formula. Based on a recent study in Southern India, the prevalence of acceptance of telerehabilitation services among stroke patients' caregivers was 92.3% (Mahmood et al., 2019). Considering some potential missing data, the estimated sample size augmented with an average of 20%. Therefore, the measured sample size was 130.

Research Instruments

This study used a validated questionnaire adapted from previous studies, which aimed to assess the awareness and perception of telerehabilitation, acceptability of using telerehabilitation services and confidence level in using telerehabilitation technology. Section 1 of the questionnaire assessed the demographic background of participants while Section 2 asked about their awareness and perception of telerehabilitation (Ullah et al., 2021). Then, Section 3 assessed their acceptability level in using telerehabilitation (Collins et al., 2022). Meanwhile, Section 4 assessed their confidence level in using the different types of telerehabilitation devices for stroke patients who were under their care (Lawford et al., 2017). Section 1 and Section 2 of the questionnaire used multiple-choice closed-ended questions. Meanwhile, Section 3 and Section 4 of the questionnaire were rated on a five-point Likert scale, whereby 5 denotes "Strongly agree" and 1 denotes "Strongly disagree".

Statistical Analysis

Descriptive statistics were used to analyse the data by using Statistical Package for the Social Sciences (SPSS) (IBM Corp., Version 26, Armonk

USA). All data obtained were cross-tabulated to obtain the frequency and percentages presented in the form of a table, pie chart or clustered stacked bar chart. As data did not achieve the normality assumption (Shapiro-Wilk test $p < 0.001$), Spearman correlation analysis was used to assess the correlation between confidence level in using telerehabilitation technology and their acceptance level to telerehabilitation. The value of $p < 0.05$ was deemed to be statistically significant.

RESULTS

Socio-Demography

A total of 152 caregivers participated in the survey. Most caregivers were between 30 – 39 years old (50.0%), followed by 40 – 59 years old (24.3%) and 24 – 29 years old (17.8%). Many caregivers were female (76.3%) and had a diploma (38.2%) or bachelor's degree (35.5%). Table 1 provides an overview of the respondents' characteristics.

Awareness and Perception of Telerehabilitation

A total of 72 (47.4%) caregivers were aware of the telerehabilitation technology but had not used it. Meanwhile, 33 (21.7%) caregivers were aware of the telerehabilitation technology and have used it on an intermittent basis. However, only one (0.7%) caregiver had good knowledge of telerehabilitation and used it regularly. Forty-six (30.3%) caregivers did not know about telerehabilitation at all. In addition, 66 (43.4%) caregivers believed that telerehabilitation could deliver consultation, and prescription, enable the delivery of required therapy and monitor. Meanwhile, 48 (31.6%) caregivers believed that telerehabilitation could also include the delivery of complex therapies. On the other hand, 38 (25.0%) caregivers expressed their uncertainty about services which can be offered by using telerehabilitation. The majority of caregivers perceived that

telerehabilitation service is socially acceptable in Malaysia, whereby 17 (11.2%) participants deemed that it was extremely acceptable, 65 (42.8%) participants perceived that it was very acceptable while 62 (40.8%) participants perceived that it was somewhat acceptable and only 8 (5.3%) participants did not perceive that telerehabilitation was socially accepted in Malaysia. Interestingly, only 65 (42.8%) participants perceived that telerehabilitation is cost-saving, while the rest of the participants thought it may incur similar expenses (16.4%) or more than the face-to-face rehabilitation expenses (17.8%). On the other hand, 35 participants (23.0%) were unsure of the financial cost of telerehabilitation services. Table 2 summarises the distribution of awareness and perception of the stroke patients' caregivers to telerehabilitation.

Acceptability Towards Telerehabilitation

Figure 1 demonstrates the overall acceptance level distribution of telerehabilitation amongst stroke patients' caregivers. Results showed that the majority of caregivers demonstrated a positive attitude to telerehabilitation, whereby 31 (20.4%) caregivers demonstrated very high acceptance and 61 (40.1%) demonstrated high acceptance. Meanwhile, 38 (25.0%) caregivers showed a neutral attitude towards telerehabilitation acceptance, 19 (12.5%) had low acceptance and only 3 (2.0%) were with very low acceptance.

Confidence in the Telerehabilitation Technology

Based on Table 2, the preferred telerehabilitation mediums among caregivers were smartphones (45.4%) and laptops (42.8%) as compared to smart televisions (7.9%) or hand-held tablets (3.9%). When asked about the confidence level of different telerehabilitation technology mediums, the majority of caregivers subsequently showed high confidence in using the smartphone (50.0%) as compared to laptop (32.9%), desktop computer (29.6%) and

hand-held tablet (21.1%). However, only 39 (25.7%) of caregivers showed high confidence in using video call service via the smartphone to deliver or receive telerehabilitation services for their stroke patients. Figure 2 summarises the confidence level distribution among stroke patients' caregivers in using different telerehabilitation technology mediums.

Correlation Study

Table 3 shows poor to fair significant linear relations between the acceptance level of telerehabilitation and confidence level in using smartphones ($rs = 0.243, p = 0.003$), video call services ($rs = 0.312, p = 0.000$) and laptops ($rs = 0.193, p = 0.017$) as compared to desktop computer and hand-held tablet.

DISCUSSION

Stroke commonly results in long-term cognitive and functional disability in patients. Therefore, the main goal of rehabilitation therapy is for stroke patients to regain independence in their daily activities and improve their quality of life (Nor Azlin et al., 2016). As medical caregivers provide coordinated multidisciplinary rehabilitative care, family caregivers also play a significant role in assisting and motivating stroke patients during therapy sessions. Therefore, the success of telerehabilitation depends on the cooperation between these two types of caregivers in facilitating the recovery process. Similarly, findings from previous studies on Malaysian urban district populations reported that there were more female caregivers for stroke patients as compared to male caregivers (Hussain et al., 2014; Tan et al., 2020). This might be due to the higher prevalence of males afflicted with stroke as compared to females, aside from the norms of cultural perception amongst Asians on the social role of females as family caretakers (Chen et al., 2019; Meira et al., 2017). In this study, all caregivers had a formal education background which could be

a factor in promoting their awareness about telerehabilitation services. However, nearly half of the caregivers who joined this survey had never heard of telerehabilitation while only less than a quarter of them had experience in using the technology occasionally. Consequently, this justifies the small number of caregivers who perceived complex therapies could also be delivered via telerehabilitation aside from routine monitoring, prescription and consultation. Although telerehabilitation is not yet widely implemented in Malaysia, awareness about telerehabilitation could be further improved to instil confidence amongst Malaysians to opt for this technology in the future (Jafni et al., 2018).

More than 70% of stroke patients' caregivers in this study were aware of telerehabilitation and perceived that this technology could be acceptable to the general population in Malaysia. This may reflect their awareness of the importance of immediate and continuous rehabilitation therapy for stroke patients after hospitalisation. The emergence of the coronavirus (COVID-19) pandemic in 2020 resulted in movement restriction policies across nations. This inevitably hampered patients' access to rehabilitation in hospitals, as seen in the reduced number of acute stroke hospital admissions from 50% to 80% in some countries (Ostrowska et al., 2021). To reduce the risk of COVID-19 infection from in-clinic rehabilitation, a study in Singapore reported implementing home visits by nurses, limiting the number of scheduled appointments as well as teleconsultation and online support activities for home exercises and aphasia therapy, despite the lack of participation from disabled elderly who were not familiar with the use of online services (Venkatasubramanian, 2020). There is a growing body of literature which suggests that telerehabilitation is similarly effective as face-to-face rehabilitation in improving the daily living functions of stroke patients (Laver et al., 2020). However, only a few studies from Southeast Asian countries reported the implementation and efficacy of

telerehabilitation, particularly for post-stroke patients (Saito & Izawa, 2021; Leochico et al., 2020; Asano et al., 2021).

The high acceptance level of telerehabilitation amongst stroke patients' caregivers is indeed associated with their preference and confidence level in using video call service via the smartphone or laptop as compared to desktop computers and hand-held tablets. Amongst the four identified studies conducted to explore telerehabilitation in Malaysia, one study used a recorded exercise video for home-based therapy for stroke patients while other studies which conducted telerehabilitation for Parkinson disease, neck pain and spastic children used smartphone-based video conferencing, laptop-based video conferencing and data logging system (Redzuan et al., 2012; Chan et al., 2021; Mani et al., 2021; Zheng & Yang, 2017). Nowadays, the mobile smartphone is deemed as a necessity for communication across different sectors, especially during the COVID-19 pandemic as people need to scan the MySejahtera QR code before entering any premise (Kamaruddin & Nawi, 2020). Both stroke patients and their caregivers were already familiar with this device; hence, promoting the sense of feasibility to use it for telerehabilitation. On the other hand, several qualitative studies had reported mixed views with respect to the feasibility of using hand-held tablets during telerehabilitation, particularly regarding positioning, handling, touch-screen responsiveness and provision of clear instructions via hand-held tablets (Shulver et al., 2017; Kearns et al., 2021).

One of the anticipated advantages of implementing telerehabilitation is to reduce the cost of in-clinic rehabilitation. Interestingly, more than half of caregivers in this study were unsure or perceived that telerehabilitation might not offer a cheaper alternative than the usual in-hospital rehabilitation. The study on the impact of stroke in Malaysia by Mairami et al. (2018) reported that the cost of post-stroke care exhausted the family's financial resources,

both from the stroke patients as well as the family caregivers (Mairami et al., 2020). The caregiving responsibilities may sometimes lead to compromised working hours or in the worst-case scenario, abandonment of effective rehabilitation intervention for stroke patients. Patients are often burdened with the huge cost of physical rehabilitation which includes transportation costs to the hospital, mobility aids such as a wheelchair and nursing care/ home helper fees as some of them do not have caretakers (Akhavan et al., 2015). These are all-inclusive of the hospital consultation and physical therapy sessions, all of which financially burden the patients with adding up to a range of costs between 53.50USD to 4,591.60USD (RM218.55 to RM18,756.69) for post-stroke care in Malaysia (Akhavan et al., 2015). Therefore, identifying the technical feasibility tailored to stroke disabilities and the use of low-cost technology are the key areas to explore in future studies of telerehabilitation in low-income and middle-income countries.

Telerehabilitation is a two-way communication between the healthcare provider and stroke patients. Recent studies by Brouns et al. (2019) reported that willingness to use telerehabilitation amongst stroke patients' caregivers and their family caregivers was indeed positively associated with the expected benefits, such as reduced cost, increased motivation, adherence to therapy and health outcomes regardless of patients' knowledge to use the technology. In contrast, the medical caregivers considered factor feasibility to be the most important, particularly regarding the technological support for patients in receiving instructions to ensure that effective therapy is achieved (Brouns et al., 2019). It is also important to acknowledge the variations in factors which influence the willingness to use telerehabilitation across different cultures and healthcare systems and tailor the implementation of technology according to the end users' needs (Brouns et al., 2020).

LIMITATION

This study has some limitations for consideration when the results are interpreted. Firstly, caregivers were approached during the stroke patients' clinic appointments, which were between April 2021 and June 2021. Therefore, the study might not capture patients who did not attend hospital appointments during that time. Secondly, this study focused on caregivers who were attending public general hospitals which did not capture patients who had attended private rehabilitation clinics in the federal territory of Malaysia. However, this was the first study which provided information on caregivers' attitudes towards telerehabilitation in the federal territory of Malaysia.

CONCLUSION

In this study, the majority of caregivers surveyed were aware of telerehabilitation technology. They indicated a high acceptance level and were confident in using video call service via the smartphone for stroke patients under their care. The level of acceptability to telerehabilitation is significantly correlated with the type of preferred telecommunication medium. Telerehabilitation may offer cost-saving complementary services to enhance long-term support and rehabilitation needs for stroke patients, particularly when in-person rehabilitation is not accessible. Therefore, efforts to educate the Malaysian population on telerehabilitation service for stroke patients should continue so that they could receive the benefits, and thus improve their physical status as well as quality of life.

ETHICAL STATEMENT

Ethical approval for this study was obtained from the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia, approval number KKM/NIHSEC/ P20-2598.

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AUTHOR CONTRIBUTION

N.N.N.R., A.F.K.B., A.P.S.A., and D.S. have made substantial contributions to the conception and design, or acquisition of data, or analysis and interpretation of data. N.N.N.R., A.P.S.A., and A.F.K.B. have been involved in drafting the manuscript or revising it critically for important intellectual content. N.N.N.R. gave final approval for the version to be published.

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Table 1 Socio-demographic characteristics of the stroke caregivers

Sample characteristics		n	%
Gender	Male	36	23.7%
	Female	116	76.3%
Age	18 – 23 years old	2	1.3%
	24 – 29 years old	27	17.8%
	30 – 39 years old	76	50.0%
	40 – 59 years old	37	24.3%
	60 – 69 years old	9	5.9%
	70 years old and above	1	0.7%
Education	Primary education	6	3.9%
	Secondary education	23	15.1%
	Diploma	58	38.2%
	Bachelor's degree	54	35.5%
	Postgraduate degree	9	6.0%
	Others professional	2	1.3%

Table 2 Survey on awareness and perception towards telerehabilitation

Survey Questions	n	%
Are you aware about telerehabilitation?		
Do not aware about telerehabilitation.	46	30.3%
Aware of the technology but have not used it.	72	47.4%
Aware of the technology and use it on intermittent basis.	33	21.7%
Good awareness and use it on regular basis.	1	0.7%
In your opinion, what are the services that can be offered using telerehabilitation?		
Consultation, prescription, delivery of required therapy and monitoring.	66	43.4%
Multiple services including consultation, prescription, delivery of complex therapies, monitoring evaluation.	48	31.6%
Not sure.	38	25.0%
In your opinion, how far is telerehabilitation is socially acceptable in Malaysia?		
Not acceptable.	8	5.3%
Somewhat acceptable.	62	40.8%
Very acceptable.	65	42.8%
Extremely acceptable.	17	11.2%
What is your nearest estimate of telerehabilitation expenses as compared to face-to-face rehabilitation?		
Less than the current expenses.	65	42.8%
Same as the current expenses.	25	16.4%
More than the current expenses.	27	17.8%
Not sure.	35	23.0%
N= 152		

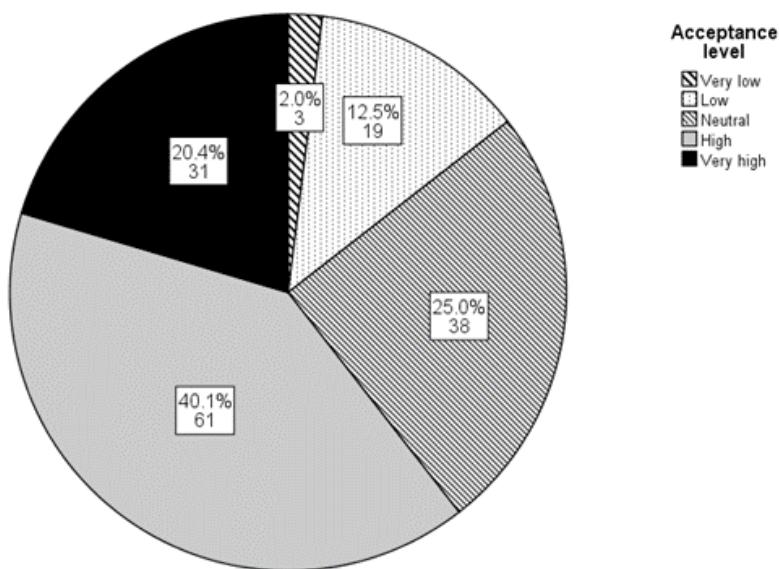


Figure 1 The acceptance levels towards telerehabilitation among stroke patients caregivers

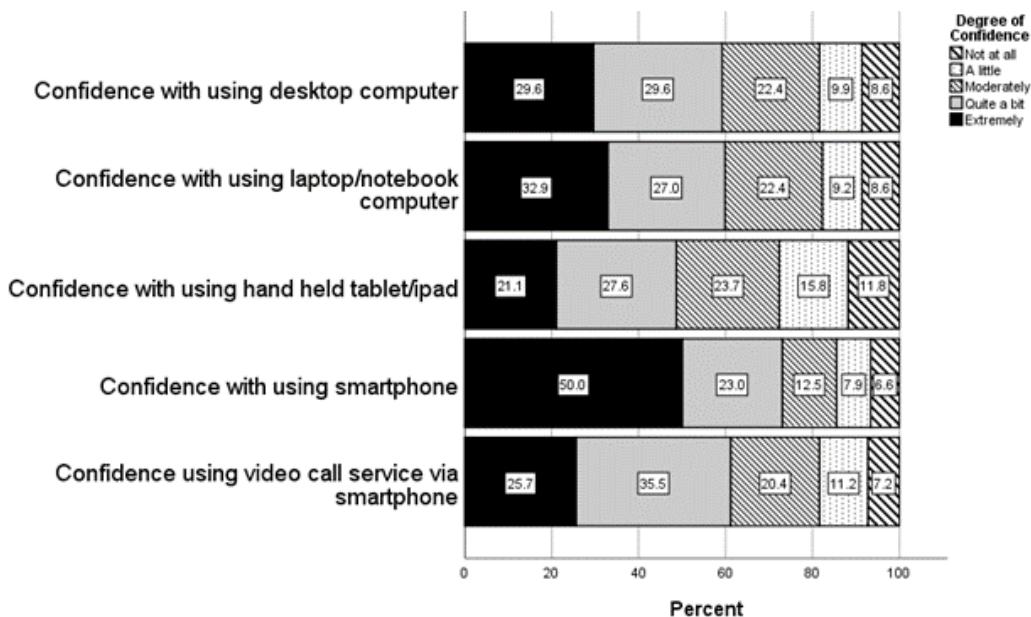


Figure 2 Confidence with technology for telerehabilitation

Table 3 Results of Spearman correlation analyses on the relationship between technology familiarity and the level of acceptance towards telerehabilitation

Characteristics	r_s	P-value
Confidence in using desktop	0.119	0.146
Confidence in using laptop	0.193	0.017
Confidence in using hand-held tablets	0.141	0.082
Confidence in using smartphone	0.243	0.003
Confidence in using video call	0.312	0.000

EDITORIAL

Meguro Parasitological Museum – A Wonderful Experience Full of Surprises

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In November 2023, one of us had the opportunity to visit the Meguro Parasitological Museum in Tokyo, Japan. The museum started its journey in 1953 with private funding from Dr Satoru Kamgeai. Now, the museum is a 70-year-old private research facility with its researchers who not only collect parasites of various animals for studies on morphology, taxonomy, distribution of parasites, etc. but also give presentations at academic meetings and publish articles in academic journals.

The museum collects and preserves about 60,000 parasite specimens (including 1,500 types). Of these, about 300 parasite specimens and related materials are exhibited in the museum, including several rare species. Medical students would certainly benefit from visiting the museum because previously, they could only study these species in medical textbooks, but now, they could see them physically. The display is divided into two categories: (i) "Diversity of Parasites", showing various types of parasite specimens with accompanying educational movies and (ii) "Human and Zoonotic Parasites", showing the life cycles of parasites and the symptoms they cause during human infection. The museum also houses 50,000 papers and 6,000 books on parasitology and parasitic diseases. In addition to research, the museum also provides educational activities and special publications. The museum offers work-study programmes and lectures and sells prepared parasite specimens for educational purposes.

There are many impressive things about the museum, including its free admission to visitors. The museum is closed on Mondays and Tuesdays, to give the opportunity for family visits with children during weekends. Unlike many other museums, taking photos is fully allowed. During the visit, the museum was full of visitors and everyone was taking photos, encouraging knowledge dissemination.

Between 1950 and 1980, Japan eliminated several major parasitic diseases (Kasai et al., 2007). Japan has achieved significant improvements in the control and prevention of parasitic infections through a school-based approach since the 1930s (Horikoshi et al., 2021). Moreover, other basic public health measures such as increased toilet use, access to clean water and avoiding the use of human excrement as agricultural fertilizer, are equally important for the control and prevention of parasitic diseases (Horikoshi et al., 2021). Countries where parasitic infections are prevalent might benefit from following these procedures. In Malaysia, several parasitic infections are prevalent (Ahmed et al., 2011; Eichenberger et al., 2020; Chuah et al., 2019; Azira et al., 2013), which need to be addressed properly and efficiently. Institutional participation and community engagement for the control of parasitic infections are vital and a parasitology museum could enrich education and awareness. Due to its distinct location among the Malaysian states, Sabah needs to address the burden of parasitic infections in the region. One of the ways is to step forward to establish a parasitology museum, addressing related issues and helping to control parasitic infections.

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ORIGINAL ARTICLE

Health-Related Quality of Life (HRQoL) and Its Associated Factors Among Post-COVID-19 Patients at Three Months in a Tertiary Hospital of Bangladesh

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ABSTRACT

COVID-19 is a burning issue brought on by the SARS-CoV2 coronavirus. Many SARS-CoV-2 survivors continue to experience a variety of symptoms, which negatively impact their standard of living. A total of 103 post-COVID patients participated in a prospective comparison study from July 2021 to December 2021 to assess the individual's health-related quality of life (HRQoL) and the elements that contribute to it. A control group with age and gender that matched 110 seemingly healthy individuals was also included for comparison. At three months, the EuroQol 5-dimensional 3-levels (EQ-5D-3L) questionnaire, which encompasses a brief expressive system questionnaire and an EQ-VAS visual analogue scale, was collected in a predesigned datasheet. The EQ index score was used to reflect all HRQoL data, which was then contrasted to a set of matched controls for ages and sexes. At three months, the mean EQ-5D index and EQ-VAS scores were lower than those of age and gender that matched the control group, at 0.810 ± 0.208 and 73.240 ± 11.36 , respectively. Regarding dimensions of the questionnaire, mobility, self-care, usual activities, pain/discomfort, and depression/anxiety were assessed at three months follow-up. The mobility and usual activity parameters showed a statistically evident difference (p -value = 0.001) compared to the control group.

INTRODUCTION

COVID-19 is a distinctly transmissible ailment brought on by the SARS-CoV2. Both an economic and a novel healthcare crisis emerged (Rubin et al., 2020). At the end of 2019, Wuhan city, in the Chinese province of Hubei, reported the first case of COVID-19. Since then, the illness rapidly spread over the world, affecting 220 nations (Worldometer, 2021). On 11 March 2020, the WHO designated it to be a pandemic illness (Cucinotta & Vanelli, 2020). The first three cases were made public by Bangladesh's Institute of Epidemiology Disease Control and Research (IEDCR) on 8 March 2020.

The broad family *Coronaviridae* contains encapsulated positive-sense single-stranded RNA viruses called coronaviruses. Along with other mammals and bird species, they can also infect humans. Coronavirus infections in both humans and animals can lead to respiratory and gastrointestinal disorders (V'kovski et al., 2021).

The SARS-CoV-2 is a member of the Beta coronavirus family, which includes the MERS and SARS viruses that cause severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). Many survivors of SARS-CoV-2 infection present with impaired lung function that lasts for months to years after being released from the hospital (Xie et al., 2005). According to research, several variables, including age, smoking status, length of hospital stays and co-morbidities, such as diabetes, hypertension, and chronic lung diseases, may contribute to the blooming of post-COVID problems (Tsampasian et al., 2023). The potential medium- and long-term effects that COVID-19 survivors may endure are not well understood. Acute COVID-19 infection survivors experience a range of physical and mental health issues, including exhaustion, trauma-related stress disorder, despair, anxiety, and sleeplessness. These issues negatively impact a patient's well-being (Arab-Zozani et al., 2020).

Health-related quality of life (HRQoL) is receiving more attention as a result of social, economic, and healthcare service improvements. A multifaceted notion, the welfare of life often involves the subjective progression of parts of life, both good and bad. HRQoL is the concept of one's perceived physical and mental health over time. Furthermore, gaining new insights into the link between HRQoL and risk variables is important. Estimating HRQoL helps determine the impact of avoidable illness and infirmity (CDC, 2021).

Following hospital release, survivors of COVID-19 may have a variety of needs, including physical, neuro-psycho-social, and social needs, according to National Health Service (NHS) England (2020) (Halpin et al., 2021). A follow-up study discovered that hospitalized SARS and MERS survivors had reduced quality of life, indicating that the effects of COVID-19 were probably going to be comparable (Ahmed et al., 2020). A separate study on post-COVID patients conducted in Iran found a significant impairment of HRQoL (Arab-Zozani et al., 2020). There is a paucity of data available regarding post-COVID patients. So, this study aims to assess the health-related quality of life in post-COVID patients and to identify the association of factors contributing to this and, therefore, to ensure better health.

MATERIALS AND METHODS

Study Design and Setting

This prospective observational research project was carried out in the COVID-19 unit and the Department of Respiratory Medicine from July 2021 to December 2021.

Sample Size Calculation

The following formula was used to determine the sample size:

$$n = \frac{(u+v)^2(\sigma_1^2 + \sigma_0^2)}{(\mu_1 - \mu_0)^2}$$

Where,

n = for measurement of different dimensions, the expected sample size

u = the predictable error, usually set at 1.96 at a 5% level, which correlates with 95% confidence level

v = 0.84 at 80% power

σ_1 = 1.0 [SD for Comparison group]

σ_0 = 0.2 [SD of EQ-5D-5L Index in study population] [Arab-Zozani et al., 2020]

μ_1 = 0.9 [Mean of Comparison group] [Yang et al., 2018]

μ_0 = 0.6 [Mean of EQ-5D-5L Index in study population] [Arab-Zozani et al., 2020]

So, the sample size for this study would be:

$$n = \frac{(1.96 + 0.84)^2 \times (1^2 + 0.2^2)}{(0.9 - 0.6)^2}$$

$$= 98$$

After using drop out formula, the sample size was:

$$N = 1 - d$$

Here, $n = 98$

$d = 10\%$ or 0.1 (Marginal error was taken 10%)

$$N = 98 / (1 - 0.1) = 108.9 \approx 110$$

So, a total of 110 patients were selected as a case.

Another 110 age-sex matched apparently healthy people who did not have any symptoms of COVID-19 infection such as fever, cough, shortness of breath, fatigue, diarrhea etc. and were not known to have been in close contact with COVID patients from the community were selected as the control group after obtaining their consent.

Sample size: The total sample size was 220 according to selection criteria.

Study Participants

The subjects of the study were recruited according to the inclusion and exclusion criteria.

Inclusion Criteria

1. All patients who had a history of laboratory-confirmed SARS-CoV-2 infection by RT-PCR.
2. Age 18 years and above.
3. Previously hospitalized for COVID-19 disease.
4. At least three months after the onset of initial COVID-19 symptoms.
5. Patients who were willing to give informed written consent to participate in the study.

Exclusion Criteria

1. Under 18 years of age.
2. Learning impairment or other impartial or conveyance impairment.
3. Pregnancy

Sampling Technique

Sampling was done using a probability (random) sampling technique for both groups.

Data Collection

For this investigation, patients who were hospitalized in the COVID unit and had their SARS-CoV-2 infection confirmed in the lab by RT-PCR were taken into account. When a patient was discharged from the hospital, they were all evaluated for eligibility. Patients who were qualified for the trial and were open to taking part were enrolled. During discharge from the hospital, information about the demographic variables (age, sex, occupation, education, smoking status) was recorded in a

data sheet. The presence of any co-morbidities, like diabetes, hypertension, chronic kidney disease, ischemic heart disease, and pre-existing lung disease were also documented by history. Three months after the onset of their first symptoms, patients were contacted or urged to visit the Department of Respiratory Medicine at BSMMU. HRQoL was assessed using an EQ-5D-3L questionnaire (Rabin & Charro, 2001). The EQ-VAS was used to score overall health status from 0 (utmost state of health deterioration possible) to 100 (optimal state of health attainment). The data was collected based on the EQ-5D questionnaire. For the investigation, a total of 110 COVID-19 patients with RT-PCR confirmation were used. Two patients passed away, and five could not be reached during follow-up, which was conducted three months following the start of the first COVID-19 symptoms. Finally, 103 patients were taken as the case sample. Another 110 apparently healthy people who had not suffered from COVID-19 infection were selected from the general population as a control group with matched age and sex. Considering the COVID-19 pandemic, proper health hygiene was followed strictly in each step of the data collection procedure. Both investigator and participants wore masks and maintained a social distance of as much as possible. Hand hygiene was also appropriately maintained.

EQ-5D-3L Questionnaire

EQ-5D-3L questionnaire (Rabin & Charro, 2001) is a common benchmark tool for evaluating HRQoL. The EQ-5D is utilized globally and is available in the majority of world languages (over 180 languages), including the Bangla version, through a closely monitored translation process (Herdman et al., 2003). Each EQ-5D instrument comprises an EQ-VAS and a brief, detailed system questionnaire. Mobility, self-care, usual activities, pain/discomfort, and anxiety/depression are the five aspects of the EQ-5D-3L. Each dimension contains three levels of responses, each of which is represented by a severity level-related number (1, 2 or 3). Thus,

a 5-digit number between 11111 (having no difficulty in any of the categories) and 33333 (having serious problems in all aspects) is used to describe the health state profile of a person. A visual analogue scale that focuses on an upward trajectory is also part of the EQ-5D-3L questionnaire and ranges from 0 (the poorest possible health) to 100 (the best possible health) to determine the respondents' overall health condition. To determine a preference-based index (EQ-5D index score), the creators of the EQ-5D produced value sets using techniques like the time trade-off (TTO) valuation approach or the VAS valuation technique in various countries. This index score is calculated on a scale of 0.0 to 1.0, where 1.0 corresponds to full health. We adopted the widely used time TTO method created in the United Kingdom, UK TTO, because there was not a value set based on the TTO developed for the Southeast Asian population. Utilizing an online calculator, the EQ-5D index score was determined. A verified Bangla translation of the EQ-5D-3L and a translation certificate were obtained for this study by emailing the necessary information to EuroQol Research Foundation, Netherlands.

Ethical Permission

The Institutional Review Board of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh, granted the ethical clearance (BSMMU/2021/4783) for this prospective observational research project.

Statistical Analysis

Data collected for the study were both quantitative (Age) and qualitative (gender, smoking status, severity). They were analyzed by using both descriptive and inferential statistics. SPSS Statistics 23 was used to organize, analyze, and present the data.

Descriptive statistical methods: The arithmetic mean, a trustworthy indicator of central tendency, and the standard deviation, a valid indicator of dispersion, were used

to evaluate continuous data. Frequency and percentages were used to summarize categorical data.

Inferential statistical analysis: Means for continuous variables were compared using unpaired t-tests. Categorical variables were compared using the chi-square test. Statistical significance between groups was assessed at a 5% level of significance.

Study of relationship: Using odds ratios (ORs) and a 95% Confidence Interval, binary logistic regression was performed to examine the relationship between the dependent and

independent variables. Statistical significance was defined as a p-value of 0.05.

RESULTS

The distribution of the research subjects' demographic characteristics is shown in Table 1. The age range of participants in the post-COVID group comprised the majority was 31 to 40 years old, followed by 41 to 50 years old. In both the post-COVID patients' group and the control group, the distribution of participants by age group was statistically comparable (p = 0.999). Age and sex differences between participants in the two groups were not statistically significant.

Table 1 Distribution of the study participants according to demographic characteristics (N= 213)

Socio-demographic characteristics		Post-COVID patients n ₁ =103(%)	Control Group n ₂ =110(%)	p-value
Age	18- 30	18 (17.5)	20 (18.2)	
	31-40	22 (21.4)	24 (21.8)	
	41-50	19 (18.4)	20 (18.2)	
	51-60	18 (17.5)	20 (18.2)	^a 0.999 ^{NS}
	61-70	17 (16.5)	16 (14.5)	
	≥71	9 (8.7)	10 (9.1)	
	Total	103 (100)	110 (100)	
Gender	Mean± SD	48.25 ± 17.07	46.85 ± 16.90	^b 0.549 ^{NS}
	Male	59 (57.3)	63 (57.3)	^a 0.999 ^{NS}
	Female	44 (42.7)	47 (42.7)	

^a chi square test, ^b Independent sample t test

s = significant, ns = non-significant

Data were as expressed as mean ±SD, frequency, and percentage.

The distribution of the study participants according to co-morbidity is presented in Table 2. Hypertension and diabetes mellitus were the more prevalent co-morbidity in post-COVID patients. Based on their co-morbid condition, the participants in both groups were statistically indifferent.

Table 2 Distribution of the study participants according to co-morbidity

Comorbidity	COVID-19 survivors n ₁ =103	Control group n ₂ =110	p-value
Hypertension	33 (32.0)	27 (24.5)	0.224 ^{NS}
Diabetes mellitus	38 (36.9)	33 (30.0)	0.286 ^{NS}
Cardiovascular disease	9 (8.7)	14 (12.7)	0.384 ^{NS}
Chronic kidney disease	14 (13.6)	9 (8.2)	0.379 ^{NS}
Preexisting lung disease	15 (14.6)	11 (10.0)	0.221 ^{NS}

^aChi square test

s = significant, ns = non-significant

Data were as expressed as frequency and percentage.

At a three-month follow-up, the post-COVID patients' frequency distribution of EQ-5D-3L dimensions and levels is shown in Figure 1. Mobility issues and pain/discomfort dimensions were the most often mentioned dimensions, followed by some difficulties doing daily activities.

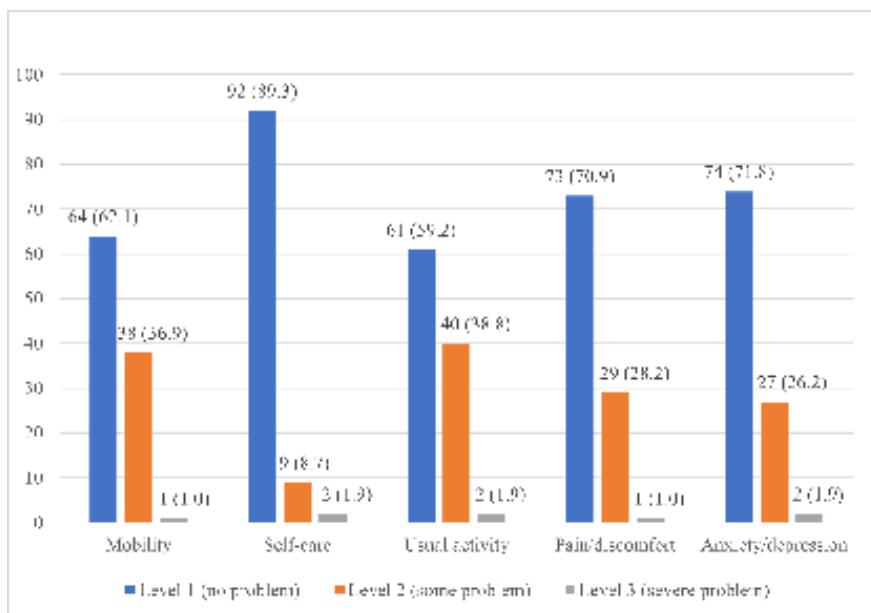


Figure 1 Frequency distribution of EQ-5D-3L dimensions and levels of post-COVID patients at three months follow-up.

The frequencies of the EQ-5D-3L dimensions and levels in the control group and post-COVID patients are shown in Table 3. There was a statistically significant difference in the participant distribution for various levels of mobility and the usual activity dimension between the post-COVID patient group and the control group ($p = 0.001$).

Table 3 Frequency distribution of EQ-5D-3L dimensions and levels in post-COVID patients and control groups

EQ-5D-3L	Post-COVID patients (3 months) $n_1 = 103$	Control Group $n_2 = 110$	p-value
Mobility	Level 1 (no problem)	64 (62.1)	$<0.001^s$
	Level 2 (some problem)	38 (36.9)	
	Level 3 (severe problem)	1 (1.0)	
Self-care	Level 1 (no problem)	92 (89.3)	0.096 ^{ns}
	Level 2 (some problem)	9 (8.7)	
	Level 3 (severe problem)	2 (1.9)	
Usual activity	Level 1 (no problem)	61 (59.2)	$<0.001^s$
	Level 2 (some problem)	40 (38.8)	
	Level 3 (severe problem)	2 (1.9)	
Pain/discomfort	Level 1 (no problem)	73 (70.9)	0.884 ^{ns}
	Level 2 (some problem)	29 (28.2)	
	Level 3 (severe problem)	1 (1.0)	
Anxiety/ depression	Level 1 (no problem)	74 (71.8)	0.949 ^{ns}
	Level 2 (some problem)	27 (26.2)	
	Level 3 (severe problem)	2 (1.9)	

^aChi-square test

s = significant, ns = non-significant

Data were as expressed as frequency and percentage.

Table 4 presents the EQ-5D-3L index scores and the EQ-VAS scores of post-COVID patient group and control group data. The median EQ-5D-3L index score (TTO index score) varied significantly between the groups ($p = 0.002$). The median EQ-VAS value also varied significantly between the groups ($p = 0.001$).

Table 4 EQ-5D-3L index scores and EQ-VAS scores of post-COVID patients and control groups

EQ-5D-3L index		Post-COVID patients $n_1 = 103$	Control group $n_2 = 110$	p-value
TTO index	Mean \pm SD	0.810 \pm 0.208	0.883 \pm 0.171	
	Median	0.848	1.00	0.002 ^s
	Range	-0.037 - 1.00	0.193 – 1.00	
VAS	Mean \pm SD	73.240 \pm 11.367	81.950 \pm 8.569	
	Median	70.00	80.00	<0.001 ^s
	Range	50 -100	55.00 – 100.00	

^aMann-Whitney U test

s= significant, ns= non-significant

Data were as expressed as mean \pm SD, median, range.

Table 5, along with the EQ-5D-3L index scores, shows the post-COVID patients' (severe and non-severe) EQ-VAS scores at follow-up. The median EQ-5D-3L index score (TTO index score) showed a difference of statistical significance between persons who were severe and those who were not ($p = 0.004$). The median EQ-VAS value for patients with severe and non-severe diseases differed significantly ($p = 0.002$).

Table 5 EQ-5D-3L index scores and EQ-VAS scores of post-COVID patients (severe and non-severe COVID-19) at three months follow-up.

EQ-5D-3L index Non severe (n=87)		Post-COVID patients (Follow-up)		p-value
		Severe (n=16)		
TTO index	Mean \pm SD	0.829 \pm 0.200	0.707 \pm 0.229	
	Median	0.850	0.743	0.004 ^s
	Range	-0.037- 1.00	0.082- 1.00	
VAS	Mean \pm SD	74.62 \pm 10.75	65.75 \pm 12.041	
	Median	75	61	0.002 ^s
	Range	50- 100	50 -100	

^aMann-Whitney U test

s = significant, ns = non-significant

Data were as expressed as mean \pm SD, median, range.

Demographic characteristics (sex, smoking), comorbidities (Hypertension, diabetes mellitus, cardiovascular disease, CKD, preexisting lung disease), severity and hospital stay were considered in the adjusted logistic regression analysis for five dimensions of HRQoL (Table 6). The presence of diabetes, pre-existing lung disease, cardiovascular disease, and severity of COVID-19 during infection, was significantly and independently associated with some degree of problem in different dimensions of EQ-5D-3L.

Table 6 Relationship between HRQoL dimensions and expected factors

Dependent variable	Independent variable	β	Odds Ratio	95% CI of ODDs Ratio		p-value
				Lower	Upper	
Mobility	Sex (male)	.152	1.165	0.434	3.123	0.762
	Hypertension	-.470	.625	0.189	2.062	0.440
	Diabetes mellitus	1.208	3.347	1.082	10.357	0.036 ^s
	Cardiovascular disease	.919	2.507	0.376	16.725	0.342
	CKD	.403	1.496	0.239	9.385	0.667
	Pre-existing lung disease	.213	1.237	0.280	5.465	0.779
	Smoker	1.169	3.219	0.736	14.071	0.120
	Severity	2.141	8.506	0.803	90.064	0.075
	Length of hospital stay (>10 days)	-.612	.542	0.126	2.330	0.411
	Self-Care	1.753	5.772	1.159	28.741	0.032 ^s
Usual activity	Pre-existing lung disease	3.161	23.590	1.948	285.598	0.013 ^s
	Severity	-2.681	.068	0.006	.800	0.032 ^s
Pain/Discomfort	Length of hospital stay (>10 days)	1.447	4.248	1.319	13.678	0.015 ^s
	Diabetes mellitus	1.665	5.286	1.733	16.117	0.003 ^s
Anxiety/depression	Diabetes mellitus	1.667	5.298	1.074	26.141	0.041 ^s
	Cardiovascular disease					

s = significant

DISCUSSION

The effect of COVID-19 infection on HRQoL and its contributing factors was investigated in this prospective observational analytical study. A total of 220 study participants aged 18 years and above were enrolled for this study from June 2021 to December 2021. Among them, there were two groups. One group consisted of 103 post-COVID patients (seven participants failed to follow-up); in another group, 110 healthy people, who did not suffer from COVID-19, were included for comparison.

In this study, patients aged 31 to 40 made up the largest proportion of participants (21.4%), followed by those aged 41 to 50 (18.4%). The majority of people in the control group (21.8%) were between the ages of 31 and 40. The two groups' average ages were

48.25 17.07 and 46.85 16.90 years, respectively. Because of this, both groups' means of age were nearly equal. In this study, males made up 57.3% of both groups while females made up 42.7%. These results matched those of studies by Shah et al. (2020), Sudre et al. (2021), and Zhou et al. (2020), among others.

Between the post-COVID and control groups, respectively, diabetes mellitus (36.9% versus 30%) and hypertension (32% versus 24.5%) were frequent co-morbid diseases. These results agreed with those of other research conducted by Huang et al. (2020) and Toussie et al. (2020). However, these results contradict with the study findings by Zhou et al. (2020), where hypertensive patients were 30% and diabetes was 19%. In this study, smoking was present in just 22.3% of post-COVID patients. Due to the lower percentage

of smokers, logistic regression analysis could not find a connection between smoking and decreased HRQoL in post-COVID patients. This result was in line with the research conducted by Farsalinos et al. in 2021. There was a hypothesis in Farsalinos' study that nicotine's ability to reduce inflammation via the nicotinic cholinergic system would make it protective against COVID-19. Smoking stimulates the synthesis of the angiotensin-converting enzyme-2 (ACE2) receptor, making smokers potentially more susceptible to this condition than non-smokers, according to Brake et al. in 2020. Smoking's impact on the severity of COVID-19 is still debatable.

In the study, the mean EQ-5D-3L index score of post-COVID patients during follow-up (at three months) was lower than that of the comparison group. Similarly, the mean EQ-VAS that represented the patient's own assessment of their health was lower than that of the control group. Both the difference in the median EQ-VAS value and the difference in the median EQ5D-3L index score between the two groups were statistically significant ($p < 0.002$ and $p < 0.001$, respectively). These findings were in agreement with another study of post-discharged COVID patients done by Garrigues et al. (2020).

The EQ-5D questionnaire is a reflective measurement of mobility, self-care, usual activities, pain or discomfort, and psychological symptoms like anxiety or depression, so the clinically significant decline seen in this study reflects the impact of the illness on HRQoL and the health burden on the country's economy. According to the percentage of people reporting issues affecting their HRQoL in each EQ-5D-3L component, typical activity (38.8%) was the most prevalent issue at the 3-month follow-up, followed by mobility (36.9%) and pain/discomfort (28.2%). However, the mobility and normal activity dimensions revealed statistically significant changes compared to the reference group ($p = 0.001$). These findings concur with those of a different study conducted by Meys et al. (2020) and Halpin et al. (2020).

In our study, univariate analysis revealed that co-morbid conditions such as diabetes, hypertension, chronic kidney disease, pre-existing lung disease, prolonged hospitalization (> ten days), and severe COVID infection were linked to poor mean EQ-5D-3L index scores ($p = 0.05$). The mean EQ-5D index score was different in patients with severe COVID-19 than in instances without severe COVID-19, perhaps because these patients had more severe COVID-19-related difficulties. In comparison to patients without diabetes mellitus, diabetic individuals had lower EQ-5D index scores. This may be because the disease progresses more rapidly in these patients, worsening their diabetes symptoms (Arab-Zozani et al., 2020). According to a different theory, hyperglycemia may play a part in the regulation of immunological and inflammatory responses, predisposing patients to severe COVID-19 and hence, potentially significant morbidity and mortality (Lim et al., 2021). That reveals that these factors may have a role in reduced HRQoL.

The presence of diabetes, pre-existing lung disease, cardiovascular disease, and the severity of COVID-19 during infection were all significantly and independently associated with some degree of problem in different dimensions of the EQ-5D-3L reflecting impairment HRQoL in our study ($p < 0.001$ and $OR > 1$), according to binary logistic regression analysis.

The current study had several limitations. First, this was a single-centered study. Second, there was a lack of information on HRQoL before acute COVID-19 illness. Third, during COVID-19 pandemic, the chance of asymptomatic COVID-19 infection in comparison group could not be ruled out completely. Finally, we used the UK crosswalk value set to estimate the EQ-5D-3L index score for post-COVID patients and comparison group. To our knowledge, a specific set of EQ-5D-3L for the Bangladeshi population has not been developed.

CONCLUSION

Our study showed that the HRQoL of post-COVID-19 patients was impaired at three months from their initial onset of symptoms compared to the average population. The most frequently reported problems were impairment in doing usual activities, followed by difficulties in mobility. Poor HRQoL was significantly related with the presence of several factors including severe COVID-19 infection and comorbidities like diabetes, pre-existing lung disease, and cardiovascular disease. Our findings would certainly spark interest among national and international communities of researchers and guide policymakers in developing and providing post-acute medical, psychological, and physical rehabilitation services to enable recovery from COVID-19 infection and, therefore, ensure the ability to return to work.

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REVIEW ARTICLE

Escape from Original Home: Do Metastatic Cells Stay Dormant or Destructive?

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ABSTRACT

Metastasis is defined as tumour implants discontinuous with the primary tumour. It is responsible for most cancer-related mortality. Many factors relating to the tumour and host factors are involved in the presence of metastasis and the long-term prognosis of the disease process. This study observed available literature and aims to emphasise tumours and their interaction with the tumour microenvironment. Epigenetic and genetic influences on pathogenesis, tumour and microenvironment interaction, role of epithelial-mesenchymal transition in metastasis are essential determinants of advanced malignant diseases. Early detection of metastatic disease is an essential part. The histopathological aggressiveness of a tumour and its biological behaviour determine the probability of metastasis and advanced disease. Understanding these factors has a benefit to improving the current therapies and diagnostic approaches to an advanced level, leading to the prevention of metastasis and more successful management of patients.

INTRODUCTION

Local invasion and metastasis constitute the primary hallmark of malignant neoplasms. Metastasis contributes to 90% of cancer-related mortality worldwide due to its effect and failure of cancer chemotherapy. The word metastasis comes from a Greek word meaning

a change, which prefixes the word stasis meaning an equilibrium state. Dissemination of cancer cells into the circulation can occur parallel or linear with the development of primary tumours. A unique subset of the cancer cell population forms metastasis-initiating cells (MICs) during the clinical course. MICs escape from the primary site disseminate in the bloodstream and overcome its pressure forces. These disseminating tumour cells (DTCs) enter the bloodstream as circulating tumour cells (CTCs) meet the challenges of the new microenvironment and local immunity of the secondary site before seeding there. Disseminating tumour cells (DTC) may remain in the secondary site as a dormant form for months to years or produce instantaneous and overt tumour formation. Depending on this, the latency period between the initial diagnosis and recurrence of metastasis may vary between different individuals.

Genetic and epigenetic signature of cancer cells and their metastatic clones

Tumour cells are genetically heterogeneous within a tumour (Welch, 2019). Intra-tumoral heterogeneity (ITH) represents the clonal evolution of a tumour and its progression. Even though malignant cells are monoclonal in origin, intratumoral genetic heterogeneity develops due to multiple mutations during their clonal evolution, leading to subclones with different biological characteristics. Initially, transformed cells resulted from inherited or acquired mutations that impaired DNA repair, and they are genetically unstable and prone to be affected by random spontaneous mutations in subsequent clonal evolution. The resultant genetic heterogeneity or diversity leads to different clonal genetic architecture within the subclones with variable behaviour, such as subclones capable of survival, growth, invasion and metastasis. Some studies explain the role of genetic heterogeneity in the clonal evolution of tumours. In the clonal evolution of plasma dyscrasia, genetic heterogeneity of selective clones undergoing primary genetic

events such as hyperdiploid and chromosomal abnormality results in clonal expansion of plasma cells, which is called gammopathy of undermined significance (MGUS) or smouldering multiple myeloma which are pre-malignant conditions. Secondary genetic events such as MYC rearrangement, TP53 mutation, or DNA repair alteration results in malignant condition (multiple myeloma) (Petrilla, 2023). By studying ITH during lateral growth and downward growth (invasion) of tumour evolution, the hierarchy of ITH was seen as early and late branching subclones along the phylogenetic tree. It was observed that early clones with less aggressive potential spread horizontally, whereas later, more aggressive subclones led to deeper and more distant spread (Ryser, 2020).

A variety of genetic contributions is needed for the development of a tumour. Carcinogens can induce normal cells to undergo genetic changes called initiating or first-drive mutation. Additional driver mutations contributing to cancer hallmarks result in precursors with stem cell-like properties and later acquire hallmarks of cancer. Additional genetic evolution can form the subclones within a tumour. The resultant intratumoral subclones, known as phenotypic heterogeneity, differ in a given phenotype. Neoplasms having ITH result in different parts of a tumour having different phenotypes and behaviours, resulting in treatment unresponsiveness with poor outcomes and progression to the advanced stage (Jacquemin, 2022).

Epigenetic heterogeneity, such as DNA methylation, can cause changes in the behaviour and outcome of a tumour (Hunter, 2018). Tumour environments such as hypoxia, pH, oxygen availability, cytokines secreted by the microenvironment immune cells, and nutrient supply can influence epigenetic change (Flavahan, 2017), resulting in epigenetic changes such as aberrant DNA methylation. This results in abnormal control of the cell cycle, DNA damage repair, and

cancer-related signalling pathways that can, in turn, cause transcriptional changes and abnormal structure of DNA or chromatin, which are the early changes in tumour formation. Epigenetic dysregulation results in aberrant epigenetic changes, usually occurring in the early stage of cancer development. Commonly encountered epigenetic changes are DNA methylation, histone modification, and chromatin conformation during cancer initiation, progression and metastasis (Guo, 2019). Epigenetic changes can contribute to the onset of tumorigenesis by altering the expression pattern of transcriptional genes (transcriptional heterogeneity) (Jacquemin, 2022). Diverse routes drive towards epigenetic aberration during tumour progression and metastasis formation, giving rise to eITH (epigenetic intra-tumour heterogeneity) (Beyes, 2021). For example, epigenetic modifications result in tumour cells' adaptation to changing developmental or environmental needs. Subclones that acquire epigenetic heterogeneity, which develop within a primary tumour, acquire propensity to relapse, therapy resistance, dissemination and immune evasion. The aberrant epigenetic changes may serve as early detection, prognostic and chemo-sensitive markers in cancer. A large cohort study of IDH-wild-type glioblastoma cases revealed the presence of widespread epigenetic heterogeneity in DNA methylation (Klughammer, 2018). Disruption of the epigenetic regulator by mutation leads to the altered transcriptome, multiplying the effects of a single genetic alteration.

Large numbers of cancers show aneuploidy (Molina, 2020), microsatellite instability or chromosomal instability (Tijhuis et al., 2019) and telomere dysfunction (Makki, 2015), which are responsible for carcinogenesis and metastasis. During the early phase of carcinogenesis, human cells acquire mutations which alter their phenotypes, and repeated mutations will form new clones. Such clones expand to grow autonomously and disseminate to distant sites. Preexisting well-established

oncogenic mutations in heterogeneous cancer cell populations such as KRAS and BRAF are associated with metastatic capability without additional mutation (Jacob, 2015).

Gene signatures of metastatic cells that enable them to survive in the journey of metastasis are derived from tumour subclones with microsatellite instability or CpG island methylation phenotypes (Setaffy, 2015). RNA binding proteins (RNABPs) such as LIN28A and LIN 28B are overexpressed and correlated with tumour invasiveness and unfavoured survival and recurrent colorectal cancers (Chatterji et al., 2018). These early mutations are supplemented with additional driver genes, such as MUC4 and SRC, for metastasis in tumour evolution (Masoodi, 2020; Poturnajova, 2020).

Cancer stem cells (CSC), a subpopulation of cancer cells, can undergo multi-lineage differentiation and self-renewal properties (Ayob, 2018). CSCs play a role in spread, recurrence and resistance to primary chemotherapy (Zhou, 2017). CSC markers such as ALDH1 and CD26 expression are correlated with tumour angiogenesis, tumour progression and metastatic capacities (Ng, 2022), and these CSC markers, Notch1 and ALDH1, are associated with perineural invasion, advanced disease in lymph nodes and recurrence (de Freitas, 2021). Dynamic bidirectional plasticity of tumour cells, which are interchangeable between CSC and non-CSC states, is required for metastasis. Colonic cancer cells with leucine-rich repeat-containing G protein-coupled receptor Lgr5⁺ (Lgr5), which initiate tumour, change into Lgr5⁻ cells for metastasis, survival in their journey and seeding in the niche sites. These Lgr5⁻ cells regain their Lgr5⁺ states to continue the expansion of secondary microscopic seeding into larger metastatic clusters (Ganesh, 2020). The extent of plasticity may be determined by epigenetic modifications such as DNA methylation and histone modifications (Kumar et al., 2022). Enzymes such as DNA methyltransferases that modify epigenome are genetically altered in

malignancies, such as *DNMT3B* in pancreatic and breast cancer cells (Yuan et al., 2019).

The journey of metastatic cells and their behaviour at secondary sites

Dissemination of tumour cells to distant sites involves a cascade of events. With the effect of genetic mutation and environmental carcinogens, neoplastic cells grow at the primary sites. For survival and growth, tumour angiogenesis is an essential process which may vary in extent based on the tumour type. Metastasising tumour cells may have the same molecular features as the primary or different properties from those at the primary site (Poturnajova, 2021; Welch, 2019). For their survival in a new site, MICs possess properties for autonomous renewal chemotherapy resistance.

Vascular endothelial growth factor receptor (VEGFR2) and endothelial receptor tyrosine kinases TIE1 and TIE2 are core signatures that regulate pro-angiogenic VEGF and angiopoietin signalling (Lugano, 2020). Mutant clones of tumour-initiating cells capable of migration also proliferate at high rates. They invade through nearby stroma by individual cells or in collective migration (Welch, 2019). The balance between antitumour immune functions and protumour (budding) determines the extent of tumour spread.

Large numbers of cancer cells are shed in the bloodstream daily, but only < 0.1% of tumour cells metastasise (Fares, 2020). The metastasising cells must leave their original sites through the basement membrane. Metastatic cells can re-infiltrate the original tumour (self-seeding) and metastasis to metastasis spread. Many processes are occurring in TME, including matrix degradation and acquired adjustment of cytoskeletal activity. Membrane protrusions called invadopodia have high proteolytic properties, enabling the cancer cells to invade the dense scaffold of stroma (Augoff, 2020;

Welch, 2019). Cancer cells produce ECM niche periostin and tenascin C to transform fibroblasts in MET into cancer-associated fibroblasts (CAF) that promote invasion and metastasis (Asif, 2021). TGF signaling render CAFs secrete cytokine such as IL-11 to activate STAT3 signaling to intensify the ability of metastatic cells to survive in secondary sites (Lai, 2020). Cancer cells optimise their environment during their journey to secondary sites by increasing NADPH through various pathways to overcome oxidative stress (Hayes, 2020). Tumour cells form emboli among themselves or with some platelets and immune cells within the circulation or acquire certain mesenchymal traits through epithelial-mesenchymal (EMT) (Makki, 2015). EMT enables invasive front cells to have better motility ability to degrade extracellular matrix than epithelial cells (Poturnajova, 2021).

After surviving the haemodynamic forces within the vessels and reaching niche secondary sites, tumour cells arrest in areas of microcapillaries start their extravasation and settle as microfoci at the site to remain dormant or progressive to form macroscopic tumours (Welch, 2019). Early Metastatic cancer cells show cancer-derived specific microRNAs (miRNAs) that can modify the tumour microenvironment (Loo, 2016) and the level of mRNAs correlated with grading and recurrences (Fletcher, 2019) and suggested miRNAs as a prognostic biomarker and deregulated mRNAs are used as trials in cancer treatment (Chakraborty, 2021).

Colorectal cancers with microsatellite instability CRC can initiate a MHC-mediated immune response of T cells, thus showing more intralesional lymphocyte infiltration (Taylor, 2022). EMT transcription factors, including SNAI1, ZEB1 and TGF- β , have been shown to suppress the functioning of the immune system of TME (Wu, 2020). Immune surveillance functions at the tumour microenvironment (TME) account for more than half of the arrested metastases (Cheng,

2020). Some genetic expression controls the dormancy of metastatic cancer cells. Genes such as *Cfh*, *Gas6* and *Ogn* are up-regulated in dormant breast cancer cells compared to proliferative cells (Ren, 2022).

After settling in secondary sites, tumour cells remain as non-detectable single cells or tiny clusters of quiescent cells in a dormant stage before the development of macrometastasis (Blasco, 2022). The balance between proliferation rate and cell death determines the time of awakening of cellular dormancy. In addition, there is a necessity for maturation with further genomic alteration to form overt cancer, which explains the latency of detectable secondary formation (Klein, 2020).

Organotropism and Metastasis

Various cancers display different spread patterns and preferred locations for secondary seeding. Cells that can intrigue the mechanical permissiveness of the capillary endothelial barrier will seed at the target distant organs. Endothelial cells (ECs) vascular endothelial growth factor (VEGF) regulates angiogenesis and new vessel formation and it is up-regulated in human cancers. ECs control the transmigration of circulating tumour cells, an important step in spreading tumour through surface receptor expression. ECs are divided into subpopulations based on their morphology and functions (Hennigs, 2021). Colorectal cancers most likely metastasise to the liver due to their fenestrated endothelial cells of liver sinusoids, allowing higher permeability of cancer cells (Martin, 2022). It may be explained by the fact that metastasis is a possibility of the anatomical location and sharing portal venous system between the organs. One theory explains that a rich sinusoidal network and slow blood flow through the liver make it more permeable to cells and other metabolites (Mielgo, 2020).

Pre-metastatic niche concept postulates that chemoattractants, extracellular vesicles (EVs) and growth factors produced by primary tumour cells may modify and prime the tumour microenvironment such as increased vascular permeability and matrix remodelling to enhance the seeding and growth (Dong, 2021). Cancer-derived EVs elicit pro-inflammation and profibrotic reactions after being taken up by tissue macrophages, leading to fibrous tissue formation and supporting further metastasis (Taboada, 2022). Due to their important role in metastasis, therapeutics that inhibit EV bio-formation and secretion may be an alternative to cancer treatment.

The research found an interaction between the brain's blood-brain barrier (BBB) and circulating breast cancer cells (BCC). Invadopodia formation of BCCs by FAK and β 4-integrin favours the invasion of distant tissues and BBB endothelial remodelling with cytoskeleton, leading to paracellular intra and transcellular permeability (Godinho et al., 2021). This fact explains why metastasis commonly occurs in the brain instead of having a highly selective blood-brain barrier. Early Metastatic cancer cells show cancer-derived specific microRNAs (miRNAs) that can modify the tumour microenvironment (Loo, 2016).

Metabolic reprogramming is an adaptive change used by cancer cells to survive. Cancer cells can induce the expression of OXCT1 enzymes for ketone metabolism, rendering the ketones usable for energy and progression (Hwang, 2022). This study stated that dietary intervention with keto diets may target metabolic changes and give benefits as a support for chemotherapy. The metabolic phenotype of a tumour is determined by genetic mutation through oncogenic signalling pathways. Conversely, oncogene-driven metabolic programming also affects the metabolism-related gene expression. Modifying these epigenomic-metabolic interactions enhances cell proliferation even in conditions with restricted growth factors and

metastasis (Goncalves, 2018). Organ-specific metabolic adaptations render the cancer cells to survive in distant organs as organo-tropic phenotypes (Schild, 2018).

Histologic grading influencing the staging of cancer

Histologic grading is a simple method to determine the disease prognosis. Its reproducibility and strong correlation with disease prognosis are demonstrated in 1813 breast cancer patients (Boiesen, 2000). Morphological features with immunohistochemical studies help to improve the prediction values for prognosis. Cell proliferation markers such as Ki-67 protein, positive for all cell cycles except for resting cells S phase and phosphohistone H3 (PHH3), showed great promise (van Steenhoven et al., 2022). Artificial intelligence helps to better assess the metastatic lymph node status, mitoses counting and facilitates expert communications (Kim, 2022). These tests are comparable to an expert pathologist without time pressure and constraints. Molecular and gene profile studies are new tools to predict tumour behaviour. They give added value to classic biomarkers for the decision to start adjuvant therapy and facilitate expert communications (Gyanchandani, 2016). Many malignant tumours, regardless of early diagnosis, complete resection and staging at the time of diagnosis, can give rise to either local recurrence or distant metastasis. Standardised pathological reports, using newly developed algorithms and report systems for large cancer registry data, provide more precise information on cancer behaviour and epidemiology of sites of metastasis (Soysal, 2017).

Epithelial-mesenchymal transition (EMT) and its role in metastasis

Epithelial-mesenchymal transition (EMT) is a cellular process which plays an essential part in cancer progression and advanced

disease. After initiated by signalling through growth factors, Notch ligands, and tumour microenvironment factors such as hypoxia, cancer cells acquire phenotypical and biological behaviour changes into mesenchymal cells, which is called epithelial-mesenchymal plasticity. The expression of N-cadherin virement histologically evidences cancer cells undergoing EMT in cancer progression as mesenchymal markers and suppression of E-cadherin and cytokeratin as epithelial markers (Jørgensen, 2020; Makki, 2015). These transformed mesenchymal cells lose their cellular adhesion and acquire strong cytoskeleton, favouring more resistance to sustained injury during migration. Through EMT, cells acquired an increased ability to migrate and invade tissues by changing cell polarity from basal-apical to frontal polarity (Jung, 2019). Epigenetic regulators such as methylation of E-cadherin (CDH1), a calcium-dependent cell adhesion protein seen in most cancers, are the EMT process's main regulators. Downregulation of E-cadherin triggers partial EMT and increases the migratory of human embryonic stem cells (hESC) (Aban, 2021). In addition, EMT endows cancer cells with resistance during cancer chemotherapy.

Ferroptosis is a cell death induced by lethal lipid peroxidation. Epigenetic reprogramming of E-cadherin of EMT process inhibition may modify the cancer cell plasticity. Studies showed that therapy-resistant cancers are associated with a mesenchymal or metastatic property, and they are more susceptible to ferroptosis inducers. Ferroptosis is also regulated by E-cadherin-mediated intercellular interaction, resulting in suppressing ferroptosis. This suggests E-cadherin inhibition or EMT induction in cancer cells might enhance ferroptosis. Experiments showed CDH1 down-regulation increases the ferroptosis susceptibility in cancer cells, showing epithelial markers, whereas overexpression of CDH1 reduces the susceptibility (Lee, 2020).

Advanced diagnostic strategies

Molecular alteration in cancer genes results in the formation of cancer driver genes and non-driver mutations. Cancer-driver genes have acquired mutations commonly linked to cancer initiation, progression and metastasis and have selective advantages, whereas non-driver genes lack this property. These driver genes can be identified and predicted risk by computational methods. Such computational predictors use data sets and predict cancer pathogenic and non-pathogenic somatic mutations (Feizi, 2022). Methods are generally based on mutational frequency for mutation significance, functional impact of mutation and structural consequences (Active Driver) (Reimand, 2013). Network analysis for identifying pathways creates a gene network for each patient. It detects the minimal set of mutated genes controlling the maximal differentially expressed (Guo, 2018) and functional multiomic integration to predict response to treatment and cancer subtypes (Pham, 2021). The identified driver genes are listed in data sets such as the network of cancer genes (NCG) and database (Repana, 2019) and Fl-net (Gu, 2020).

As metastasis is a most dangerous tribute of malignancy, it is mandatory to exclude metastasis at first diagnosis before the decision of treatment and at follow-up visits. A new non-invasive test in clinical oncology is the liquid biopsy, which uses blood or body fluids such as urine or pleural fluid to detect circulating tumour cells (CTCs), DNA (ctDNA), or tumour extracellular vesicles. The tumour's molecular profile is obtained through single or repeated sampling by liquid biopsy, and individually personalised therapy can be arranged for real-time monitoring of therapy and screening for chemotherapy resistance in the management course (Lone, 2022). Precise genomic atlas for various cancers provide more information on the molecular profile of the tumour and is advantageous for the decision of treatment modalities such as targeting angiogenesis

or triggering cancer death by apoptosis (Li, 2021). CTCs can be tested for intra and inter-patient variable expression of epidermal growth factor receptor (EGFR)-related genes like KRAS and PIK3CA to determine colorectal cancer response and therapeutic outcomes (Luo, 2020).

A rapid autopsy is a post-mortem examination performed on an urgent basis after the death of a patient. Large and adequate tissue samples can be taken from many body sites at autopsy and are analysed for molecular sequencing, proteomic analysis or immunological analysis in various types of cancer. This procedure allows the study of the diseases after aggressive local or distant spread. A sufficient amount of tissue sampling enhances the study by multiple disciplines (Hooper, 2021). Scientists discovered a new strategy for patients' avatars using animal avatars, xenografting in immunocompromised mice models or in vitro 2D cell line cultures. This method can provide multidisciplinary studies on tumour behaviour and treatment response based on genomic, proteomic and epigenetic analysis are now in advance (Fazio, 2020).

Minimal residual diseases (MRDs) are multicellular secondary tumour cell clusters or disseminated single tumour cells (DTCs) after treatment. The aim of detecting MRD is to monitor response to therapy and possible relapse (Kruse, 2020). MRD is assessed by detecting phenotypes or gene expression using flow cytometry, polymerase chain reaction or next-generation sequencing. Multiple levels of MRD testing are used to identify risk profile for adjusting the chemotherapy duration. The molecular sequencing method detects cell-free circulating tumour DNA (ctDNA) after neoadjuvant systemic therapy in triple-negative breast cancer. Several study results showed that ctDNA positivity rate and 3-year event-free survival and overall survival are positively correlated (Stecklein, 2023). Advances in multidisciplinary sections such as clinical, pathology, and laboratory

investigations are crucial for comprehensively treating primary and secondary malignancies (Parker, 2022).

CONCLUSION

The study of key biological features and the process of disease progression of malignant tumours is essential for predicting prognosis and management plans. Identifying high-risk patients who can develop metastasis is challenging in real practice. Further research should be performed to understand more about the role of genetic and epigenetic factors, biological behaviour of tumours and their reactions with tumour environment in progression of disease. Understanding the mechanism of advanced disease and ways to detect it before well-established seeding in distant sites will help improve existing treatment, leading to more effective, timely control of malignant diseases.

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SHORT COMMUNICATION

Postgraduate Nursing Education in Malaysia and Advanced Nursing Practice: Where Are We and What's Next?

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ABSTRACT

The nursing profession plays a pivotal and indispensable role in the promotion of public health, disease prevention, and comprehensive care delivery to diverse populations. As in other healthcare-related fields, the continuous development of nursing education assumes paramount importance in addressing the myriad challenges posed by the modern era. This paper presents a thorough examination of the historical origins, current status, and future prospects of postgraduate nursing education in Malaysia, encompassing a thorough exploration of its evolution. Furthermore, the study critically examines the interface between postgraduate nursing education and advanced nursing practice within the healthcare landscape of Malaysia. By analysing these dimensions, this paper contributes to a deeper understanding of the strategic enhancements necessary for further strengthening the nursing profession in the country.

INTRODUCTION

The nursing profession in Malaysia plays a vital role in promoting health, preventing disease, and delivering quality patient care. To ensure the competence and preparedness of nursing professionals to meet the evolving demands of healthcare, postgraduate nursing education assumes a critical role. This paper seeks to analyse the current status of postgraduate

nursing education in Malaysia, assess the challenges faced, and propose strategies for the future of advanced nursing practice in the country.

Historical Perspective

Nursing is a major workforce in the healthcare system (Fawaz, Hamdan-Mansour & Tassi, 2018). Preregistration in nursing is at a bachelor's degree in many parts of the world, especially in Western countries. Meanwhile, there are two types of preregistration nursing education (basic) in Malaysia, namely, a Diploma and a bachelor's degree. While Diploma holders account for the majority of Malaysia's nursing workforce, the bachelor's degree programme only began in 2003. In the Malaysian context, the next steps for nursing specialisation are Post Basic in nursing (6-month course) or Advanced Diploma (12-month course), which are also called post-registration programmes in speciality areas. Most of these programmes are offered by the Ministry of Health and some private higher education institutions (Ministry of Higher Education, 2010). To date, diploma holders are the majority in the nursing workforce, while 'fresh' degree holders have limited positions in Malaysian government hospitals (Ellin & Che Hassan, 2022).

Current Landscape of Postgraduate Nursing Education

The postgraduate nursing education landscape in Malaysia has seen significant progress over the last two decades. Three public universities, namely the University of Malaya (UM), Universiti Teknologi Mara (UiTM), and the National University of Malaysia (UKM), led the way by offering specialised programs with a focus on clinical practice. These programs aimed to produce graduates who could apply their expertise in teaching and delivering quality care to clients (Ministry of Higher Education, 2010). Currently, postgraduate nursing education in Malaysia offers a diverse range of specialised programs, including clinical specialties, leadership, and

management. While some programs have gained recognition, others face challenges due to resource constraints and limited faculty expertise. There is a need to align these programs with emerging healthcare trends and technological advancements.

Nurses in Malaysia have ample opportunities to pursue postgraduate education, with both public and private universities offering various master's nursing degrees. The Ministry of Health supports continuing education by providing study leave and allowances to successful applicants. While public universities such as UM, UiTM and UKM began to offer master's in nursing degrees in 2010, other private universities, including MAHSA University College and Open University, are also offering nursing-related courses at the master's level (Ministry of Higher Education, 2010). At the latest, a total of 25 master's and Doctor of Philosophy (PhD) programmes in nursing-related fields are open for applications in the academic 2023/2024 session (Ministry of Health Malaysia, 2023). Public universities such as Universiti Sains Malaysia (USM), International Islamic University Malaysia (IIUM), and Universiti Malaysia Sarawak (UNIMAS) and a few more private universities have been added to the list. Malaysia's Ministry of Health also supports continuing education among Malaysian nurses by providing study leave, allowance, or *Hadiyah Latihan Persekutuan* to successful applicants (Ministry of Health Malaysia, 2023).

Despite the progress, it remains unclear to what extent the initial objectives of postgraduate nursing education have been achieved in both the educational and service sectors. However, the increasing number of nursing-related programs available for the upcoming academic session indicates positive growth in the field. Continued efforts to improve and adapt these programs to meet the evolving demands of healthcare will further enhance the landscape of postgraduate nursing education in Malaysia.

Challenges Faced by Aspiring and Practicing Nurse Professionals

Aspiring and practising nurse professionals encounter various obstacles in pursuing postgraduate education. Financial barriers, limited research and publication opportunities, and inadequate recognition for advanced nursing practice are key challenges. The absence of a clear career progression pathway and insufficient support for continuing professional development may also hinder nurses' motivation to pursue higher education.

Despite the availability of Master of Nursing degree programmes, most graduates end up in education and administration roles rather than providing direct patient care. This deviates from the initial goal of producing nurses with expert content to teach and provide clinical care. Encouraging nurses with at least a bachelor's degree to work in government hospitals and then supporting their pursuit of master's degrees in specialised areas could be a step forward where currently limited/no posts for advanced nurse practitioners available (Ministry of Higher Education, 2010; Mohd Ariffin & Che Hasan, 2022). A recent study revealed that Malaysian nurses with bachelor's degree qualifications have significantly higher critical thinking scores compared to nurses with a post-basic/advanced diploma in nursing and certificate/diploma in nursing ($p = 0.003$) (Daphne et al., 2020).

A disparity exists in the clinical functions of nurses providing patient care, primarily based on their qualifications. While U29 nurses, comprising diploma holders with or without post-basic qualifications, carry out clinical functions at 80% capacity, their U41 counterparts, possessing degree qualifications with or without post-basic qualifications, are operating at a capacity of only 70% (Ministry of Health Malaysia, 2021). Additionally, the availability of U41 nurses is severely restricted, with less than ten nurses of this category typically present in each hospital.

Furthermore, the roles of U29 and U41 nurses predominantly revolve around routine care. This situation raises concerns about optimising the utilisation of nursing resources and the distribution of specialised care and advanced roles within healthcare institutions.

Advanced Practice Nurses (APNs), including CNS and Nurse Practitioners, require a minimum master's degree (Wheeler et al., 2020) and play crucial roles in advancing care and research (Ministry of Higher Education, 2010). Master of Nursing degrees in Malaysia should target practice nurses with a bachelor's degree and a strong clinical focus. For instance, IIUM offers Master of Advanced Nursing Practice programs in Critical Care, Emergency Care, and Renal Care, aligning with the Ministry of Higher Education expectations in 2010.

Given the complexities in healthcare, there is a growing demand for nurses with critical thinking abilities and advanced skills to address challenges effectively (Hooper, 2014; Daphne et al., 2020). To meet the expectations of APN roles, developing a practice-focused Doctor in Nursing Practice (DNP) curriculum instead of solely research-focused PhD programmes would be beneficial. This would equip nurses with the necessary competencies to navigate the evolving healthcare landscape successfully.

What's Next for Postgraduate Nursing Education

To enhance postgraduate nursing education in Malaysia, several crucial strategies should be put in place. Firstly, it is important to strengthen the partnership between academic institutions and healthcare facilities to promote research and clinical exposure. Secondly, it is necessary to develop standardised and accredited postgraduate nursing programmes to ensure consistent and high-quality education. Thirdly, it is to reiterate the imperative of addressing a pressing concern to the government regarding the heightened engagement of nurses with

higher educational qualifications in hospital settings, particularly in roles that encompass well-defined clinical functions parallel to those of advanced practice nurses. In this context, there is a call for an intensified focus on research initiatives aimed at scrutinising the effects of such involvement on patient care outcomes. To advance this critical endeavor, it is suggested that research activities be channelled through capstone projects facilitated within the framework of Master of Advanced Nursing Practice programmes and PhD projects that are directly aligned with the enhancement of patients' well-being. This approach promises to provide invaluable insights into the tangible impacts and advantages of integrating highly educated nurses into the healthcare system, ultimately promoting superior patient care and overall healthcare system efficiency. Finally, leveraging technology and incorporating digital health components into the curricula will equip nurses to thrive in the increasingly technologically advanced healthcare industry.

CONCLUSION

In conclusion, Malaysia can overcome the challenges and seize the opportunities in postgraduate nursing education to create a robust system that produces highly skilled, specialised, and technologically proficient nursing professionals with the right approach. The future of postgraduate nursing education in Malaysia relies on acknowledging and legitimising the significant role of advanced nursing practice. Healthcare policies should emphasise the contributions of nurse practitioners, clinical nurse specialists, and nurse educators, leading to a more clearly defined career path for nursing professionals. Prioritising advanced nursing practice and investing in nursing education will undoubtedly lead to an improvement in the quality of healthcare services across the country.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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CASE REPORT

An Uncommon Aetiology of Native Valve Infective Endocarditis: *Corynebacterium glutamicum* Infective Endocarditis

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ABSTRACT

Corynebacterium glutamicum is a rare cause of infective endocarditis increasingly identified as a pathogen causing significant morbidity and mortality. We report a middle-age female with underlying end-stage renal failure who developed *Corynebacterium glutamicum* catheter-related bloodstream infection and eventually succumbed. This case highlights the importance of recognizing *Corynebacterium* as an emerging nosocomial pathogen and early management to improve clinical outcome.

INTRODUCTION

Corynebacterium are gram-positive, catalase-positive, aerobic or facultatively anaerobic organisms. They are generally non-motile rods. The genus can be subdivided into the *Corynebacterium diphtheriae* and the non-diphtherial *Corynebacteria* species. Non-diphtherial *Corynebacteria* is generally considered as part of the normal human skin and mucus membranes. Thus, when isolated from clinical specimens, they are frequently dismissed as contaminants. Nonetheless, they have been increasingly identified as pathogenic over the past two decades, especially in patients with immunodeficiency state such as malignancy or chronic diseases (Coyle et al., 1990; Chen et al., 2012).

CASE PRESENTATION

A 37-year-old woman with underlying end-stage renal failure (ESRF) on regular haemodialysis was admitted due to bleeding from her arteriovenous fistula (AVF) post dialysis at her haemodialysis centre. Her bleeding from the AVF had stopped upon arrival at the hospital and she was transfused with packed red blood cells due to severe anaemia (haemoglobin of 5.2 g/dL) (Table 1). A temporary femoral dialysis catheter was inserted while her AVF was put on rest. Unfortunately, she developed fever on day 3 of admission with pus discharge noted from her arteriovenous fistula. Ultrasound of the AVF demonstrated collection with possible partial thrombosis of the AVF. She was started on empirical intravenous ampicillin-sulbactam 1.5g twice a day. Due to her fever, her femoral dialysis catheter was removed on day 3 of admission with blood cultures obtained from both lumens prior removal.

Her blood cultures grew *Corynebacterium* species. Microbiology assessment of biochemical set and comparison with Vitek 2 Automated System were performed to identify the species of *Corynebacterium*. From the biochemical set, the organisms were catalase and urease positive. They were able to ferment glucose and maltose. All the isolates were reverse Camp test positive with *Staphylococcus aureus*. *Corynebacterium glutamicum* was identified with a probability of 96%. Possibility of the organism being contaminant was lowered as the repeated blood cultures three days apart from periphery and both lumens of the femoral dialysis catheter grew the same organism. Unfortunately, drug sensitivity test was not done. Due to her persistent spiking fever, a transthoracic echocardiogram was ordered and showed a vegetation over her posterior mitral valve leaflet with presence of moderate mitral regurgitation (Figure 1a & 1b). The size of vegetation was $\pm 0.8 \text{ cm}^2$. She had no physical stigmata of infective endocarditis. She was switched to intravenous benzylpenicillin 4 mega unit twice a day for her *Corynebacterium*

glutamicum catheter related blood stream infection and infective endocarditis (Figure 2a). On day 12 of admission, she developed sudden onset multiple generalized tonic-clonic seizures. Computed tomography (CT) scan of the brain showed multiple acute subarachnoid haemorrhage (Figure 2b). She succumbed later that day due to sepsis from *Corynebacterium glutamicum* catheter related blood stream infection and infective endocarditis complicated with subarachnoid bleeding.

DISCUSSION

Non-diphtherial *Corynebacteria*, with the example of species including *Corynebacterium ulcerans*, *Cpseudotuberculosis*, *Corynebacterium pyogenes*, commonly colonize human skin and mucus membranes. Only lately is the pathogenicity of these organisms evident in human or even livestock infections¹. Patients at a high risk of infection include those who are immunocompromised or have co-morbidities such as HIV infection (Roig-Rico et al., 2011; Gutiérrez-Rodero et al., 1999; Roig et al., 1993), malignancies, chemotherapy (Waters, 1989; Kebbe et al., 2015) and conditions that affect their poly-morphonuclear cells function, for instance diabetes mellitus, alcoholism (Martinez-Martinez, L. et al., 1994) or end stage renal failure, as seen in our case. *Corynebacterium* spp. causes approximately 0.2 to 0.4% of native valve endocarditis and 9% of early and 4% of late prosthetic valve endocarditis (Knox et al., 2002; Riegel et al., 1996). *Corynebacterium glutamicum* is an industrial microorganism conventionally utilized for amino acids production (Gopinath et al., 2014). Although other *Corynebacterium* spp. especially *Corynebacterium striatum* has been reported to cause infection such as infective endocarditis (Bläckberg et al., 2021), we would like to highlight the possibility of *Corynebacterium glutamicum* being an important pathogen in immunosuppressed patients. There have been insufficient reports on infection caused by *Corynebacterium* species and more knowledge is required.

Traditionally, diphtheroid species are identified using cultures. They mostly require special media such as sheep's blood agar, Loeffler or tellurite plates, to grow. Communication with the microbiology laboratory is essential for appropriate processing of the cultures, as the colony types have a variety of biochemical characteristics. Lately 16S ribosomal ribonucleic acid (rRNA) probes have been invented for identification of corynebacterial genus and species. The new anaerobe and *Corynebacterium* (ANC) identification card for Vitek 2 met all performance criteria within a 95% confidence interval when compared with 16S rRNA gene sequencing reference method (Rennie et al., 2008). A multiplex PCR system can also be utilized for identification and determination of toxigenicity of corynebacterial species with zoonotic potential (Bernard, 2016; De Fátima Costa Torres et al., 2013; Sekar et al., 2017).

To date, there are still no guideline on the management of *Corynebacterium* CRBSI and infective endocarditis. Fortunately, most of the *Corynebacterium* species are sensitive to various antibiotics including penicillin and vancomycin. We think that that vancomycin would have been a better choice of antibiotic for her as she was septic. Corynebacterial species had been reported to be susceptible to vancomycin in most circumstances. There were some reported vancomycin-resistant species in the literatures (Williams et al., 1993). Among the true *Corynebacterium* species reported to have multiple antibiotic resistances are *C. xerosis*, *C. urealyticum*, *C. jeikeium*, and *C. minutissimum* (Soriano et al., 1995). Nevertheless, vancomycin is still considered the drug of choice for the treatment of corynebacterial infection until susceptibility testing has been determined (Wood, 1993). Duration of vancomycin therapy in native valve infective endocarditis is 6 weeks (Marrie et al., 1984). Numerous studies have proven that *Corynebacterium* species can produce biofilm on the surface of catheters (Baddour et al., 2015; Olson et al., 2002), which can be

less effectively eradicated by vancomycin (Darouiche et al., 1994), thus necessitate longer hospitalization for resolution of fever when removal of indwelling catheter is not performed. A study completed by S. Ghide et al. (Ghide et al., 2009) has suggested that removal of central venous catheter may not be necessary in patients with *Corynebacterial* CRBSI, especially when a non-glycopeptide antibiotic is administered.

CONCLUSION

It is crucial to recognize *Corynebacterium* as an emerging nosocomial pathogen. Although *Corynebacterium* could be isolated from a blood culture as a common contaminant, in some cases it could conceal a serious underlying infection, especially in critically unwell patients with medical devices such as central venous catheter or implanted indwelling device. Due to the patient's poor general condition and comorbidity, our patient succumbed from catheter-related bloodstream infection caused by *Corynebacterium glutamicum*.

CONFLICT OF INTEREST

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CONSENTS

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FIGURE LEGENDS

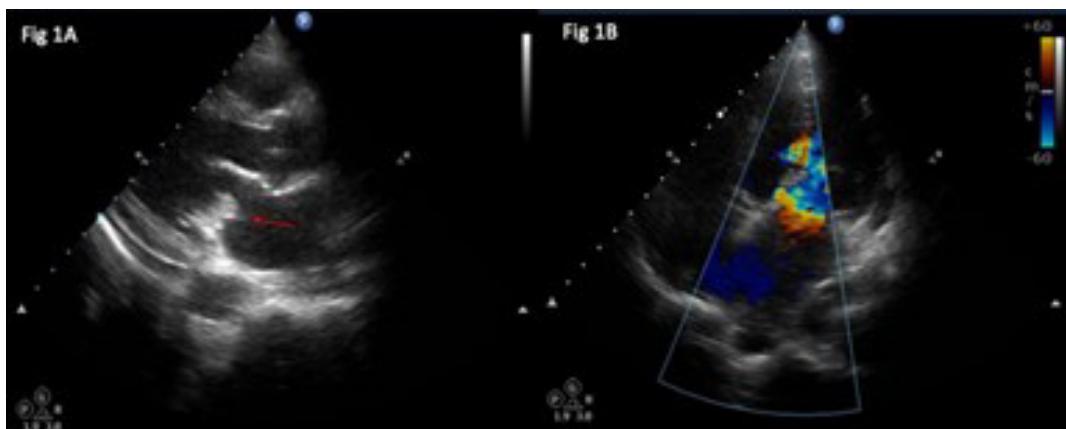


Figure 1: (A) Transthoracic echocardiogram shows a vegetation (arrow) on the posterior mitral valve leaflet (Parasternal long axis view). (B) Transthoracic echocardiogram shows moderate mitral regurgitation with colour doppler imaging in the apical 4 chamber view.



Figure 2: (A) On blood agar, *Corynebacterium* colonies form small white to cream colour non-haemolytic colonies with dry granular appearances, mostly translucent but with opaque centres, convex with continuous borders. (B) On chocolate media, *Corynebacterium* form tiny, creamy-white colonies.

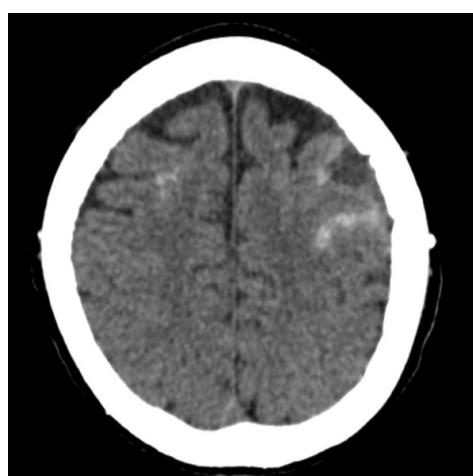


Figure 3: Plain Computed tomography (CT) scan of the brain showed multiple acute subarachnoid haemorrhages.

Table 1: Investigations

	Units	Reference range	Day 1 Admission	Day 6 Admission
Haemoglobin	g/L	135 – 176	52	98
White cell count	10 ¹² /L	4.5 – 11	6.06	8.4
Platelet count	10 ⁹ /L	150 – 410	50	113
International normalized ratio (INR)			1.29	
Urea	mmol/l	2.8 – 7.2	25.9	26.8
Sodium	mmol/l	136 – 146	129	135
Potassium	mmol/l	3.5 – 5.1	3.5	3.7
Creatinine	µmol/l	59 – 104	719	791
Total bilirubin	µmol/l	5 – 21	10.6	
Alanine transaminase	U/l	0 – 50	11	
Alkaline phosphatase	U/l	30 – 120	164	
C-reactive protein	mg/l	0 – 5	166.6	
Blood culture from periphery Day 3 of admission			<i>Corynebacterium glutamicum</i>	
Blood culture from both femoral dialysis catheter lumens			<i>Corynebacterium glutamicum</i>	
Blood culture from periphery Day 6 of admission			<i>Corynebacterium glutamicum</i>	

CASE REPORT

Helminth Infestation Causing Anaemia in Pregnancy Attending Primary Care Clinic: A Case Report

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ABSTRACT

Anaemia in pregnancy is among the commonest medical disorders encountered antenatally. However, the condition has sometimes been overlooked and not corrected accordingly given wrong or unidentified exact causes. Helminth infestation, even though rare generally nowadays, is still an important cause that needs to be ruled out in case of anaemia. We reported a case of an antenatal woman who presented with unresolved anaemia. However, she benefited from the helminth infestation screening and was able to be treated well. Her condition tremendously improved after the eradication of the infection. This case highlighted that anaemia should always include stool for ova and cyst despite no convincing history towards the infection. The symptoms could be mild or even not recognised.

INTRODUCTION

Pregnancy anaemia is characterised by decreased red blood cells or haemoglobin in the maternal bloodstream. This condition can lead to decreased tissue oxygen delivery, resulting in fatigue, weakness, and other symptoms (Frayne & Pinchon, 2019). Furthermore, anaemia in pregnancy is associated with adverse outcomes for both the mother and the developing foetus. There are many causes of anaemia in pregnancy,

such as haemodilution, maternal iron deficiency, vitamin B12 deficiency, and folate deficiency, as well as genetic disorders such as haemoglobinopathy, especially thalassemia trait (Frayne & Pinchon, 2019; Miller, 2013; Petrakos et al., 2016). Nevertheless, certain infections, such as helminth infestations, particularly hookworm, have been identified as a significant contributor to anaemia in pregnant women (Nurdiati et al., 2001; Wahed et al., 2020).

The usual workup for anaemia in pregnancies includes full blood count, iron studies, and other specific tests to determine the underlying cause of the anaemia (Frayne & Pinchon, 2019; Miller, 2013). However, screening for helminth infestations in pregnant women may not be routine, and therefore, such infestations may go unnoticed in many cases. Therefore, a specific clinical hint should be identified to screen the case earlier for better outcomes (Nurdiati et al., 2001; Wahed et al., 2020). We highlighted a case of anaemia in pregnancy that benefits from an appropriate helminth work-up despite vague hints in history and clinical presentation.

CASE PRESENTATION

A 27-year-old (Gravida 2 Para 0+1) at 24 weeks period of amenorrhea came to the primary care clinic for her regular antenatal follow-up. She complained of occasional palpitations and fatigue since early pregnancy. She had no shortness of breath, dizziness or other symptoms of anaemia. Her fetal movement was good. She had no history of vaginal bleeding, melena or blood loss. She complies with her antenatal haematinic (Zincofer), which contains 100mg of elemental iron in the ferrous form. She also has been taking her meals regularly. She has no known medical illness. She had a history of spontaneous abortion during eight weeks of amenorrhea in 2022. Her family members are well, without any history of thalassemia or anaemia.

On examination, she was alert with mild pallor. Her hydration was good. Her blood pressure was 122/71 mmHg, and her pulse rate was 101bpm. Her weight was 59kg, with a body mass index of 24kg/m². Obstetric examination revealed a singleton foetus with fundal height corresponding to 24 weeks of gestation. Other system examinations are unremarkable.

Her haemoglobin was 10.9g/dl. Her full blood count is as follows:

Table 1 Initial full blood count result.

Parameter	Result	Normal value
WBC (x10 ⁹ /L)	9.3	4.0-11.0
RBC (x10 ¹² /L)	3.78	3.9-5.6
HB (g/dL)	10.9	12.0-16.0
HCT (%)	30	35-47
MCV (fl)	73	76-96
MCH (pg)	26.7	28-34
MCHC (g/dL)	33.2	30-36
Platelet (x10 ⁹ /L)	244	150-400
RDW	14	12.4-15.1
Ferritin (ug/L)	9	11-300
TIBC (ug/dL)	88	50-170

She was compliant with her medications and high-iron diet advice. Her symptoms persist till her subsequent follow-up at 28 weeks period of gestation. Despite coming from a high-income group, with no recent travel to the seaside or sand and no concomitant gastrointestinal symptoms, we arranged for stool ova and cyst, which reveals the presence of hookworm infestation. She was treated with one course of Albendazole 400mg for three days and was given an appointment for follow-up. She remains well with good weight gain. Her haemoglobin level has increased to 11.5g/dl, as shown in Table 2. Her transabdominal ultrasound reveals normal foetal growth according to her gestational age.

Table 2 Full blood count result after deworming treatment.

Parameter	Result	Normal value
WBC (x10 ⁹ /L)	8.06	4.0-11.0
RBC (x10 ¹² /L)	4.52	3.9-5.6
HB (g/dL)	11.7	12.0-16.0
HCT (%)	41.6	35-47
MCV (fl)	92	76-96
MCH (pg)	29.5	28-34
MCHC (g/dL)	30.8	30-36
Platelet (x10 ⁹ /L)	253	150-400
RDW	14.93	12.4-15.1
Ferritin (ug/L)	38	11-300
TIBC (ug/dL)	68	50-170

DISCUSSION

Anaemia, a condition characterised by a decrease in red blood cells or haemoglobin levels in the blood, is prevalent among pregnant women worldwide (Frayne & Pinchon, 2019). The connection between malaria and anaemia in pregnancy is well-established, but recent studies have also found a correlation between helminthic infestations and anaemia during pregnancy (Miller, 2013; Nguyen et al., 2006; Nurdiani et al., 2001). Studies conducted in Indonesia have identified that 69.7% of pregnant women are infected with helminths, specifically *Trichuris trichiura* followed by *Necator americanus* (hookworm) and is a significant contributor to anaemia in the second trimester of pregnancy (Nguyen et al., 2006; Nurdiani et al., 2001).

The exact mechanism by which helminthic infestations induce anaemia in pregnancy is not clearly understood. However, it has been suggested that these infections decrease erythropoiesis by releasing nitric oxide. Nitric oxide can reduce the deformability of erythrocytes, leading to increased red blood cell destruction (Wijshake et al., 2023). Helminthic infestations during pregnancy can have several detrimental effects on both maternal and foetal health (Mpairwe et al., 2014). These infections can lead to malnutrition, iron deficiency

anaemia, and increased vulnerability to other infections in infected pregnant women (Miller, 2013; Mpairwe et al., 2014; Wahed et al., 2020). Furthermore, helminth infestations, particularly hookworm infestations, have been identified as significant contributors to severe anaemia during pregnancy in Sub-Saharan Africa (Brooker et al., 2007). Studies have shown that helminthic infestations during pregnancy, such as hookworm infestations, can cause occult or overt intestinal blood loss due to mucosal or submucosal invasion, further exacerbating anaemia (Mpairwe et al., 2014; Wijshake et al., 2023). Foetal complications such as foetal growth restriction and low birth weight can also arise (Brooker et al., 2007; Mpairwe et al., 2014).

Screening and management strategies for helminthic infestations in pregnant women are crucial to prevent and treat anaemia (Blackwell, 2016). First, stool ova and cysts should be included in the anaemia workup and made routine even if the procedure is troublesome. The management of helminth infestations, particularly in pregnancy and anaemia, requires a comprehensive approach. This approach includes both prevention and treatment strategies. Prevention measures should include education on proper hygiene practices, such as handwashing and the importance of a clean water supply. A patient from high economic status is not equivalent to good hygiene practice in which the advice should be generalised to all (Blackwell, 2016; Brooker et al., 2007; Nurdiani et al., 2001). Additionally, implementing deworming programs in endemic areas can help reduce the prevalence of helminthic infestations among pregnant women (Nguyen et al., 2006; Nurdiani et al., 2001). Treatment strategies for helminth-induced anaemia in pregnancy often involve the use of anthelmintic medications, such as albendazole or mebendazole. These medications effectively eliminate helminthic infestations and reduce the associated intestinal blood loss, thus improving anaemia (Brooker et al., 2007; Mpairwe et al., 2014;

Nguyen et al., 2006). In terms of safety, both albendazole and mebendazole are safe for use during pregnancy. Furthermore, these medications are inexpensive and readily available, making them accessible in resource-limited settings (Brooker et al., 2007; Nguyen et al., 2006).

In this case, our patient had anaemia, which was diagnosed in the second trimester. Her anaemic workup showed iron deficiency anaemia, confirmed with a low ferritin count. The uniqueness of this case is that there are no specific risk factors to suggest this patient had any worm infestation. She did practice good hygiene at home. She also had good financial resources with a high monthly income. According to our Perinatal Manual Care, local guidelines on managing anaemia in pregnancy also state that investigation for stool ova and cyst is optional and not warranted for all cases (Ministry of Health, 2013). Nevertheless, our case has benefited from a stool sample investigation given persistent low ferritin levels despite good compliance to a high iron diet and haematinics. This is a striking clue that should not be missed. Low ferritin furthermore does not favour thalassemia. The stool result shows helminth infestations, which were treated with Albendazole. Subsequently, her anaemia improved, and foetal growth is normal for gestational age.

CONCLUSION

Anaemia in pregnancy is fairly common. However, screening for causes of anaemia at primary care levels should also include screening for intestinal parasitic infestations. In some communities, opportunistic screening for intestinal parasitic infestations may benefit all antenatal women. This rare but possible anaemia cause must be suspected, especially when other common causes have been ruled out at the initial phase.

CONFLICT OF INTEREST

The authors declare that they have no competing interests in publishing this case.

CONSENTS

Written informed consent was obtained from the patient to publish this case. A copy of the written consent is available for review by the Editor-in-Chief.

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