A randomised clinical trial of the safety, cost effectiveness and patient experience of nurse-led telemonitoring of chronic hepatitis B patients

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Summary

Introduction: Chronic Hepatitis B (CHB) remains an important health concern in Singapore with approximately 3.6% population affected and remains a common condition requiring follow-up by Gastroenterologist. Virtual monitoring has been used at many centres for various diseases, however, safety, effectiveness is still not explored.

Aim: Assess if virtual monitoring of patients with CHB is safe, acceptable and cost-effective.

Methods: Prospective randomised-control trial to assess the safety, efficacy and patient satisfaction of virtual monitoring of liver tests by trained nurse-clinician. Patients were randomised to either monitoring by doctor alternating with the nurses (NHTMS), or follow-up by doctors (Control). Randomisation was by sealed envelope method. Primary clinical end point was (a) cirrhosis (b) Hepatocellular carcinoma or (c) Raised ALT requiring medications, whereas patient’s acceptance and cost effectiveness were secondary end points. Patients were asked to fill questionnaire on satisfaction and acceptance of care at 1, 2 years in the nurse-led monitoring arm. 333 patients were recruited, 311 completed 2 years follow-up.

Results: No significant difference was seen in the clinical outcome of patients in either arm with combined primary end point reached in 10 patients in each arm. However, there was significant difference in cost saved on transport with the NHTMS patients saving $20.23 on transport cost and 103 minutes of time by reducing the visits. 83.9% of NHTMS patients felt that NHTMS was better than being followed up by doctors, whereas 84.5% preferred the NHTMS model.

Conclusion: Nurse-led virtual-telemonitoring of stable CHB patients is safe, acceptable by patients and reduces cost on health care.
1 | INTRODUCTION

Chronic Hepatitis B remains a common disease in South-East Asia, with prevalence of disease being 3.6% in Singapore.\(^1\)\(^2\) Regular follow-up for is essential for early diagnosis of tumours and detection of hepatitis B (CHB) flare at an early stage. Regular follow-up of CHB consumes time and money for the patients who have asymptomatic disease resulting in high default rate and also leads to increased burden on healthcare resources due to high prevalence of the disease. In our centre approximately 15% patients default follow-up appointments as Gastroenterology clinic. Patients with Hepatitis B have, 0.8% chance of developing liver cancer every year.\(^3\)

During follow-up patients have to come to the specialist outpatient clinic once for blood tests and/or ultrasound and subsequently another time for doctors visit to know the blood tests and/or scan results, hence for each follow-up, patients end up visiting hospital twice.

To optimise the use of health care resources and reduce the frequency of visits without compromising safety of the patients various strategies have been studied including nurse-led monitoring, virtual monitoring. We used a mixed strategy of telemonitoring and regular physician visit in this model so as to optimise the utilisation of the resources.

2 | AIM

This study aims to assess if virtual monitoring of patients with chronic hepatitis B is safe, acceptable to patients and reduces cost to patients.

3 | METHODS

3.1 | Study design

A prospective non-inferiority randomised control trial with follow-up period of 2 years was used to assess the outcomes and patient experience of virtual telemonitoring of liver tests by trained nurse clinicians. Inclusion criteria were subjects that were stable as determined by primary physician with alanine aminotransferase less than two times upper limit of normal. Exclusion criteria were subjects having any of the following characteristics: age less than 21 years, cognitive impairment, pregnant or inability to speak Chinese or English. Intention-to-treat principle was adopted for this study with patients who became pregnant or developed cognitive impairment within the study period of 2 years included in the analysis.

Patients were randomised by sealed envelope method with an allocation ratio of 1:1 into Control and Nurse-led Hepatitis B Telemonitoring Service NHTMS groups. In the Control group, participants were followed up by specialists in Singapore General Hospital (SGH) every 6 months, whereas participants in the NHTMS group were followed up every 6 months with trained nurse-clinicians over the phone alternating with specialists in SGH. Blinding of group allocation was not done in the study as it was not possible for any attending physicians not to know who is on regular follow-up and who is on follow-up with NHTMS.

Study period was from 1 September 2013 to 15 June 2017, with the last subject recruited on 15 June 2015.

This study was approved by the SingHealth Central Institutional Review Board for research ethics.

3.2 | Measurements

The primary outcome for this study is safety of service and it is measured by the incidence rate of HCC, cirrhosis and deterioration of disease that calls for medication treatment determined by AASLD and EASL guidelines\(^4\)\(^5\) during follow-up of 2 years after recruitment. End point of this study was achieved if subjects had any of the above.

The secondary outcome for this study is the change in total transport expenses for appointments and waiting time for CHB appointments were examined as indirect cost saving outcomes. CHB appointments was defined as all follow-up appointments with a specialist or nurse-clinician and blood tests that were done on a different day prior to follow-up appointments. Average transport expenses and waiting time were obtained from participants and were multiplied by the number of CHB appointments at baseline for the year prior to the study and at 1-year follow-up. Change of transport expenses and waiting time were then calculated by deducting the follow-up total of each variable by the baseline total of each variable.

Patient experience was evaluated using adapted questions from the Generic Short Patient Experiences Questionnaire (GS-PEQ).\(^6\) Question 4-8 and 15 were adapted for the study based on feedback from patients during the field testing of the questionnaire. A modified version of question 15 (Did you get sufficient information about your test results?) and Q24 (Overall, was the care you received from your clinician satisfactory?) were added as additional questions. A five-point response scale was used for these questions where 1 was described as ‘Not at all’ and 5 as ‘To a very large extent’.

In addition, acceptability of NHTMS was evaluated by asking participants to compare NHMS with the standard care on a 5-point scale (‘A lot worse’ to ‘A lot better’) and their preferred CHB model of care.

3.3 | Sample size calculation

Approximately 0.5%-1% of the patients with Hepatitis B but not on treatment will develop HCC, 1%-2% will develop cirrhosis, and approximately 1%-5% per year will need medications for fluctuations in ALT and, therefore approximately 7% will achieve primary end point.\(^3\)\(^7\)\(^8\) With non-inferiority range of 7%, power of 80% and 5% significance, 143 patients will be required in each arm to assess a clinical end point. With 10% drop out rate expected, we aimed to recruit 335 patients in the study.
3.4 | Statistical analysis

Continuous variables were expressed as means and standard deviations (SD), whereas categorical variables were expressed as their numbers and percentage. Comparisons of categorical variables between control and NHTMS study arms were done using Chi-square test or Fisher’s Test. Differences of continuous variables between both study arms were compared using independent T-test. Paired T-test was used to compare NHTMS patient experience with care before and after the NHTMS service. R version 3.4.3\(^{10}\) was used for statistical analysis.

4 | RESULTS

333 participants were recruited for the study to take into account of participant drop out. Among the participants were recruited, 1 (0.3%) dropped out after randomisation, 7 (2.1%) withdrew from the study, 10 (3.0%) defaulted on their appointments, 1 (0.3%) died due to nonliver-related cause and 3 (0.9%) were lost to follow-up (Figure 1). Table 1 summarises the characteristics of 311 participants who completed the follow-up within the study period. Majority of the participants were Chinese (98.0%), female (55.3%) and were generally of middle to advanced age (53.9 ± 12.7 years). Mean baseline blood result was 2.73 ± 1.70 μg/mL for AFP, 42.4 ± 2.8 g/L for albumin and 23.7 ± 10.3 IU/L for ALT and are all within their respective reference ranges, therefore liver function of participants are normal.

4.1 | Primary outcomes

To evaluate the safety of NHTMS, comparison of key health outcomes of patients were done with results shown in Figure 2. There were no significant differences between Control and NHTMS in the proportion of patients who developed HCC (0.7% and 1.3% respectively, \(P = 1.000\)), developed cirrhosis (0.0% and 0.6% respectively, \(P = 1.000\)), and had ALT fluctuations (6.5% and 6.3% respectively, \(P = .747\)). Therefore, there was no difference between patients who achieved the end point (6.5% and 6.3% respectively, \(P = 1.000\)) during the study period.
### 4.2 Secondary outcomes

Secondary outcomes that were examined in the evaluation of the NHTMS were shown in Table 2. Among NHTMS patients, the change in transport expenses (mean difference: S$20.23, P < .001) and change in waiting time for appointments (mean difference: 103.89 mins, P < .001) were significantly lower than Control patients.

### 4.3 Experience with care

Comparison of experience with care provided by specialist-led clinic and nurse-led clinic was only done among NHTMS patients as the NHTMS service is evaluated in its totality which includes both monitoring by doctor and monitoring by nurse. As shown in Table 3 There were no significant differences between specialists and nurses in patients' ease in understanding their care provider, time for interaction, sufficient amount of information about diagnosis and test results and satisfaction from the care received. The confidence of NHTMS patients with the professional competence of the main care provider was statistically lower when it was a nurse (mean difference: 0.15, P = .013) as compared to a specialist. Similarly, the care that was shown by nurses was perceived to be significantly lower as compared to specialists (mean difference: 0.14, P = .040). Nurses were also perceived to be less interested in NHTMS patients' description.

### TABLE 1 Sample demographics and baseline blood results

| Sample Information | Whole sample (n = 311) | Control (n = 153) | NHTMS (n = 158) | P (SC vs NHTMS) |
|--------------------|------------------------|------------------|----------------|-----------------|
| Age, y, Mean (SD)  | 53.9 (12.7)            | 52.7 (12.9)      | 55.0 (12.4)    | .107            |
| Gender¹, Male, n (%) | 138 (44.7)            | 70 (46.4)        | 68 (43.0)      | .639            |
| Ethnicity², n (%) |                        |                  |                |                 |
| Chinese            | 302 (98.0)             | 148 (98.0)       | 154 (97.5)     | .616            |
| Malay              | 4 (1.3)                | 1 (0.7)          | 3 (1.9)        |                 |
| Indian             | 0 (0.0)                | 0 (0.0)          | 0 (0.0)        |                 |
| Others             | 3 (1.0)                | 2 (1.3)          | 1 (0.6)        |                 |
| Baseline blood result, Mean (SD) |          |                  |                |                 |
| AFP, µg/L          | 2.73 (1.70)            | 2.64 (1.40)      | 2.82 (1.93)    | .326            |
| Albumin, g/L       | 42.4 (2.78)            | 42.7 (2.66)      | 42.2 (2.87)    | .102            |
| ALT, IU/L          | 23.7 (10.32)           | 23.8 (11.31)     | 23.7 (9.29)    | .910            |

¹n = 311.

### FIGURE 2 Comparison of primary outcomes using chi-square/Fisher’s test.

ALT Fluctuations P = .747, all others P = 1.000. HCC stands for hepatocellular carcinoma and ALT Fluctuations were ALT fluctuations in subjects that required medications. End point was considered achieved if subjects had ALT fluctuations requiring treatment, development of HCC and/or cirrhosis.

### TABLE 2 Comparison of Secondary Outcomes using Independent t test

| Study group       | Change in transport expenses for CHB appointments, S$ | Change in waiting time for appointments, minutes |
|-------------------|------------------------------------------------------|--------------------------------------------------|
|                   | Mean (SD)                                            | Mean difference (95% CI)                          | P value |
| Control (n = 153) | -11.68 (72.50)                                       | 20.23 (2.53 to 37.93)                             | <.001   |
| NHTMS (n = 158)  | -31.91 (85.75)                                       | -168.35 (161.25)                                 | <.001   |
|                   |                                                       | 103.89 (65.39 to 142.39)                          |         |
of their situation too (mean difference: 0.24, \( P = .001 \)). This can be attributed to the type of service delivered, as virtual monitoring did not require face to face interaction, hence patients were less confident of a new service.

### 4.4 | Acceptability of NHTMS

Figure 3 shows participants’ opinions when comparing NHTMS with standard care. 52.3% of the participants felt that NHTMS was a lot better, 31.6% felt that it was a little better, 12.9% felt that there was no difference, whereas 3.2% felt that it was slightly worse. As shown in Figure 4, majority (85.4%) of the participants preferred to follow the NHTMS model of care. 3.8% preferred the current model of care, 2.5% preferred to see a specialist alternating with nurse-clinicians in SGH. Less than 2% of the participants preferred to see a specialist alternating with either type of primary care providers in Singapore (polyclinic: 1.9%, GP: 1.3%), whereas 2.6% indicated their preference for other models of care.

### 5 | DISCUSSION

A prospective randomised control study on nurse-led telemonitoring of chronic hepatitis B patients has not been reported before.

#### TABLE 3  Comparison of NHTMS patients’ experience with care using paired t test

| Question                                                                 | Mean (SD)       | Mean difference (95% CI) | \( P \) value |
|---------------------------------------------------------------------------|-----------------|--------------------------|--------------|
| Did your healthcare provider talk to you in a way that was easy to understand?\(^a\) | Specialist (n = 155) 4.56 (0.74)  | Nurse (n = 155) 4.60 (0.62)  | −0.04 (−0.17 to 0.09)  | .554 |
| Did you have confidence in your healthcare provider’s professional competence? | 4.68 (0.59)  | 4.53 (0.68)  | 0.15 (0.03 to 0.27)  | .013\(^b\) |
| To what extent did you perceive that your healthcare provider care for you?\(^a\) | 4.49 (0.73)  | 4.35 (0.70)  | 0.14 (0.01 to 0.27)  | .040\(^b\) |
| Did you perceive your healthcare provider to be interested in your description of your situation?\(^a\) | 4.52 (0.68)  | 4.28 (0.79)  | 0.24 (0.10 to 0.39)  | .001\(^b\) |
| Did you get enough time to talk and interact with your healthcare provider?\(^a\) | 4.34 (0.79)  | 4.44 (0.70)  | −0.10 (−0.24 to 0.06)  | .221 |
| Did you get sufficient information about your diagnosis/afflictions?\(^a\) | 4.45 (0.81)  | 4.30 (0.92)  | 0.16 (−0.02 to 0.34)  | .083 |
| Did you get sufficient information about your test results?\(^a\) | 4.43 (0.79)  | 4.43 (0.78)  | 0.00 (−0.16 to 0.16)  | 1.000 |
| Overall, was the care you received from your healthcare provider satisfactory?\(^a\) | 4.62 (0.60)  | 4.52 (0.60)  | 0.10 (−0.02 to 0.21)  | .092 |

\(^a\)\( n = 154; \)
\(^b\)\( Statistically significant (\( P < .05\)). \)
\(^c\)\( n = 151. \)
\(^d\)\( n = 152. \)
This is first randomised control prospective study to report the usefulness of virtual monitoring and compared with control. Nonrandomisation may lead to biased interpretation as severely diseased patients are more likely to be followed up by clinicians than virtual monitoring. In this study clinical end points were used as primary outcome to ensure that the clinical outcomes were not different when patients were virtually monitored. We also analysed the results which were monitored by nurses so as to see if any laboratory findings were overlooked. None of the significant laboratory findings were overlooked.

The patients with chronic Hepatitis B are referred to specialist centre as they have complex medical condition or need opinion for abnormal liver tests, hence requiring follow-up at specialist centre, the cohort of these patients are on follow-up at specialist centre.

Use of telemedicine has been emphasised in Europe which can potentially reduce the cost of healthcare. Previous meta-analysis from COPD on cost effectiveness have been questioned due to heterogeneous studies done on telemedicine, however, studies have demonstrated reduction in the number of hospitalisations.

Patient experience with care from nurses were poorer and could be attributed to the apprehension of their first interaction with a new caregiver. Despite their experience with care, patients still valued the convenience that the service brought which showed with the high level of acceptance (83.9%).

However, in patients with cognitive impairment virtual monitoring may be a challenge; patients with cognitive impairment were excluded from this study.

This study looks as loss of work and manpower for the patients and acceptance rate, however, the limitation of this study is that it does not consider cost increment to the hospital/country for training a nurse. As the cost of hiring a nurse clinician is much lower than a specialist physician, it is likely cost effective from the hospital point of view.

Our study confirms that properly trained nurse can supplement clinician in reducing work. This approach is acceptable to the patients and reduces the cost of health care.

CONFLICT OF INTEREST

None of the authors have any conflict of interest.

ETHICAL STATEMENT

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to and the appropriate ethical review committee approval has been received.

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FIGURE 4 Preferred hepatitis B model of care of participants for their 6-month follow-up appointments
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