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## **Readiness for hospital discharge among patients requiring home nutrition support: a cross-sectional study**

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**Running title:** HNS and readiness for hospital discharge

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## ABSTRACT

**Background and Objectives:** This study aimed to investigate readiness for hospital discharge of patients requiring home nutrition support and explore the factors that influence this readiness. **Methods and Study Design:** This cross-sectional survey included 220 patients discharged from the general surgery department of a tertiary-care teaching hospital in China with home nutrition support. Readiness for Hospital Discharge Scale and Quality of Discharge Teaching Scale scores were calculated and general and disease- and therapy-related information were collected. Univariate, correlation, and multiple linear regression analyses were performed. **Results:** The mean standardized total Readiness for Hospital Discharge Scale score was  $7.33 \pm 1.65$ , with the subscales expected support, personal status, perceived coping ability, and knowledge scoring  $7.40 \pm 1.78$ ,  $7.35 \pm 1.66$ ,  $7.30 \pm 1.73$ , and  $7.26 \pm 1.74$ , respectively. The mean standardized Quality of Discharge Teaching Scale score was  $7.48 \pm 1.59$ . The Quality of Discharge Teaching Scale score, length of hospital stay, expected length of home nutrition support, first-time use of home nutrition support, Nutrition Risk Screening 2002 score, and diagnosis were all identified as influencing factors of readiness for discharge (adjusted  $R^2=0.564$ ,  $F=14.5$ ,  $p<0.001$ ). **Conclusions:** Patients requiring home nutrition support were only moderately ready for discharge. Enhancing the quality of discharge teaching could significantly improve readiness for discharge, with more attention needed for patients who have been in hospital longer, are expected to use home nutrition support long-term, are at risk of malnutrition, are using home nutrition support for the first time, or have a digestive system malignancy.

**Key Words:** readiness for hospital discharge, discharge teaching, home nutrition support, home enteral nutrition, oral nutrition supplements

## INTRODUCTION

Home nutrition support (HNS) consists of oral nutritional supplements (ONS), home enteral nutrition (HEN), and home parenteral nutrition (HPN).<sup>1</sup> Studies have revealed the significant benefits of HNS, such as fewer hospital readmissions, lower mortality rates, maintenance of gastrointestinal integrity, and improved quality of life.<sup>2-5</sup> As a result, HNS is being increasingly widely used in China.<sup>6</sup> Patients receiving HNS must perform self-care behaviors such as HNS administration, tube maintenance, complication observation, and HNS monitoring to avoid infection, leakage, tube defects, and other adverse events.<sup>4,5</sup> Comprehensive and individualized discharge planning can help to minimize the risks of

adverse events, and readiness for hospital discharge evaluation can help to understand the effectiveness of discharge planning.<sup>7</sup>

The term readiness for hospital discharge was first used by Fenwick to refer to the ability of patients to continue the recovery process after leaving hospital.<sup>8-10</sup> It has been proposed to be essential for the successful transition from hospital to home, and is regarded as a critical component of clinical care.<sup>11</sup> The Readiness for Hospital Discharge Scale (RHDS) was created to evaluate the readiness of patients to leave hospital. It has been used in patients with a variety of conditions, such as major depressive disorder, myocardial infarction, and HIV, and those who have undergone hepatobiliary surgery.<sup>7,12-14</sup>

However, research on the readiness for hospital discharge of patients requiring HNS is lacking, and the influencing factors are unknown. Thus, this study aimed to determine readiness for hospital discharge in patients requiring HNS and identify the variables that influence this readiness, with the goal of providing evidence to support clinical practice.

## **MATERIALS AND METHODS**

### ***Study setting, design, and sampling***

This cross-sectional study used convenience sampling to recruit participants from the general surgery department of a tertiary-care teaching hospital in China. The general surgery department includes eight units specializing in the treatment of conditions such as inflammatory bowel disease, fistulas, short bowel syndrome, and acute pancreatitis, which treat patients from all over China.

The inclusion criteria were as follows: 1) discharged with HNS (ONS/HEN); 2) aged  $\geq 18$  years; 3) no mental health conditions; and 4) volunteered for this study and provided informed consent. The exclusion criteria were as follows: 1) self-discharged against medical advice; 2) hearing or cognitive dysfunction; and 3) discharged with HPN (including HPN combined with other nutritional support methods). Patients discharged with HPN were excluded from the present study as HPN remains uncommon in China and concerns remain over its safety and feasibility. If participants were unable to complete the survey independently due to literacy issues, they were aided by researchers.

Kendall's sample size calculation principle yields sample sizes 5–10 times the number of variables.<sup>15</sup> The survey used in the present study contained 27 variables: 10 related to general information, 10 related to disease and therapy, 4 related to the RHDS, and 3 related to the Quality of Discharge Teaching Scale (QDTS). Considering an invalid rate of 20%, it was determined that a sample size of 162–324 was required.

## ***Instruments***

### **General information questionnaire**

The general information questionnaire collected data on patient sex, age, marital status, educational level, work status, place of residence, living alone, access to a nearby hospital, monthly income, and medical insurance coverage.

### **Disease- and therapy-related information questionnaire**

The disease- and therapy-related information questionnaire collected data on length of hospital stay, number of hospitalizations, diagnosis, surgical procedures, comorbidities, medications prescribed at discharge, whether HNS was being received for the first time, type of HNS, expected length of HNS, and the Nutrition Risk Screening 2002 (NRS2002) score calculated before discharge. The NRS2002 is a tool for screening nutritional risk, with an overall score ranging from 0 to 6; patients scoring  $\geq 3$  points are considered nutritionally at-risk.<sup>16</sup>

### ***Readiness for Hospital Discharge Scale (RHDS)***

The RHDS, developed by Weiss et al. to evaluate readiness for hospital discharge, comprises 21 items.<sup>10</sup> This study used a short form of the RHDS, which consists of four subscales of readiness (each with two items): personal status (physical readiness and energy), knowledge (problems to watch for and restrictions), perceived coping ability (ability to handle demands at home and perform personal care), and expected support (help with personal care and help with medical care).<sup>11,17</sup> Each item was scored from 0 to 10, giving an overall RHDS score of between 0 and 80, and a standardized score (total score/number of items) of between 0 and 10. Higher scores indicate greater readiness for hospital discharge. The RHDS standardized score was categorized as follows: low ( $<7$ ), moderate (7–7.9), high (8–8.9), and very high (9–10). In this study, the total Cronbach's  $\alpha$  was 0.975, with each subscale ranging from 0.925 to 0.942.

### ***Quality of Discharge Teaching Scale (QDTS)***

The QDTS, developed by Weiss in 2007,<sup>18</sup> has been widely used to measure the quality of discharge teaching for patients.<sup>14,19,20</sup> The scale consists of 18 items in 3 dimensions: content needed (6 items), content received (6 items), and delivery skills and effects (12 items). The content needed dimension was used separately for comparison with the content received dimension but was not included in the total score.<sup>21</sup> Each item was rated on a scale of 0–10,

giving an overall QDTS score (from the content received and delivery skills and effects dimensions) of between 0 and 180 and a standardized score (total score/number of items) of between 0 and 10. Higher scores indicate greater discharge education quality. In this study, the overall Cronbach's  $\alpha$  was 0.969, with each dimension ranging from 0.943 to 0.970.

### ***Data collection***

Two researchers used the Hospital Information System to select patients according to the inclusion and exclusion criteria between December 2022 and February 2023. The general information questionnaire, disease- and therapy-related information questionnaire, RHDS, and QDTS were distributed to eligible patients within the 4 h prior to discharge and were collected on the spot. The average time taken to complete the questionnaires was 15 min.

In total, 227 questionnaires were distributed. Of these, seven questionnaires with missing items were excluded and 220 valid questionnaires were included in the analysis.

### ***Statistical analysis***

Two researchers checked and entered the data, and statistical analyses were performed using SPSS software version 27.0 (IBM Corporation, Armonk, NY, USA). RHDS and QDTS scores are presented as mean  $\pm$  standard deviation. The frequency and percentage of general information, disease- and therapy-related information, and RHDS answers are described. The RHDS scores according to general and disease- and therapy-related information were compared using independent-sample t-tests, one-way analyses of variance, Mann–Whitney U tests, and Kruskal–Wallis H tests based on the Kolmogorov–Smirnov test. Relationships between RHDS and QDTS scores were examined using Pearson's or Spearman's correlation coefficients, according to the normality of the variables. Multiple linear regression analysis was performed to identify factors influencing readiness for discharge. Statistical significance was set at  $p < 0.05$  (two-sided).

### ***Ethics approval and consent to participate***

The Institutional Review Board of Jinling Hospital, Affiliated Hospital of Medical School, Nanjing University approved our study protocol and the procedures for obtaining informed consent before the formal survey (2022DZGZR-064). This study was performed in accordance with the principles outlined in the Declaration of Helsinki. The participants were informed of the purpose of the study before providing consent and anonymity and confidentiality were guaranteed.

## RESULTS

### *RHDS scores among patients discharged with HNS*

The RHDS scores are shown in Table 1. The mean total score was  $58.6 \pm 13.2$ , and the mean standardized score was  $7.33 \pm 1.65$ , which was classified as moderate. The subscale with the highest score was expected support ( $7.40 \pm 1.78$ ), followed by personal status ( $7.35 \pm 1.66$ ), perceived coping ability ( $7.30 \pm 1.73$ ), and knowledge ( $7.26 \pm 1.74$ ).

### *QDTS scores among patients discharged with HNS*

Table 2 presents the QDTS scores. The mean total QDTS score was  $135 \pm 28.6$ , and the mean standardized score was  $7.48 \pm 1.59$ . The highest-scoring dimension was delivery skills and effects ( $7.67 \pm 1.65$ ), followed by content needed ( $7.64 \pm 1.42$ ) and content received ( $7.10 \pm 1.92$ ).

### *Univariate analysis*

As shown in Table 3, the RHDS score was significantly affected by the following general characteristics: sex ( $T=2.81$ ,  $p=0.005$ ), work status ( $F=6.25$ ,  $p<0.001$ ), place of residence ( $T=2.13$ ,  $p=0.035$ ), monthly income ( $H=10.9$ ,  $p=0.012$ ), and medical insurance coverage ( $T=2.94$ ,  $p=0.004$ ).

As presented in Table 4, the RHDS score was significantly affected by the following disease- and therapy-related information: length of hospital stay ( $H=23.7$ ,  $p<0.001$ ), diagnosis ( $H=25.8$ ,  $p<0.001$ ), whether HNS was being received for the first time ( $Z=-3.95$ ,  $p<0.001$ ), type of HNS ( $F=19.7$ ,  $p<0.001$ ), expected length of HNS ( $F=22.7$ ,  $p<0.001$ ), and NRS2002 score ( $T=3.18$ ,  $p=0.002$ ).

### *Correlation of RHDS and QDTS scores*

Spearman's correlation analysis indicated that the RHDS score was positively correlated with the QDTS score ( $r=0.620$ ,  $p<0.001$ ) and its dimensions. The subgroup analysis showed that the RHDS subscales personal status, knowledge, perceived coping ability, and expected support were significantly related to the QDTS dimensions content needed, content received, and delivery skills and effects, as well as the total QDTS score, as shown in Table 5.

### *Factors influencing readiness for discharge*

Multiple linear regression analysis identified the total QDTS score, length of hospital stay, expected length of HNS, whether HNS was being received for the first time, NRS2002 score,

and diagnosis as factors influencing the RHDS score (adjusted  $R^2=0.564$ ,  $F=14.5$ ,  $p<0.001$ ), as shown in Table 6.

## DISCUSSION

Many studies have shown that a lack of readiness for hospital discharge is associated with coping difficulties, treatment non-adherence, adverse events, and hospital readmissions.<sup>18,19,22-24</sup> Therefore, it is crucial to assess readiness for hospital discharge to accurately determine the individual needs of patients and develop tailored discharge plans. This study found that patients discharged from the general surgery department with HNS had moderate RHDS scores, which is inconsistent with the findings of other studies.<sup>11,14</sup> Weiss et al. conducted a randomized clinical trial involving patients from 33 medical-surgical units, and reported high RHDS scores before (8.42) and after (8.64) intervention.<sup>11</sup> In contrast, Qian et al. found that patients who were discharged from hospital with tubes after hepatobiliary surgery had low RHDS scores ( $6.45\pm 1.09$ ).<sup>14</sup> This variation may be attributed to regional and population differences between these studies. In the present study, the RHDS subscale knowledge was the lowest ranked. This finding is consistent with those of previous studies in China,<sup>7,21,22,25</sup> but differs from those of studies conducted in other countries.<sup>26-28</sup> This indicates that the health education provided in Chinese hospitals is insufficient to meet the knowledge requirements of patients. Therefore, education sessions are recommended throughout the hospitalization period, rather than only on the day of discharge.

A previous study reported that most patients' overall ability to obtain medical resources after discharge was unsatisfactory, again highlighting the significance of discharge education.<sup>29</sup> In the present study, the QDTS score was moderate, with the content received dimension scoring less than the content needed dimension, suggesting that patients felt that the discharge teaching provided was not comprehensive. There are two possible explanations for this observation. First, most patients (55.5%) in this study were receiving HNS for the first time. They lacked relevant knowledge and experience and had high expectations that medical staff would provide all the necessary information. Second, the general surgery department includes eight units. The management and provision of discharge teaching may be primarily disease-specific, with less of a focus on general issues such as HNS, information about which is usually provided in a non-standardized manner based on the time and availability of healthcare providers and patients. Therefore, a multidisciplinary Nutrition Support Team (NST) is undoubtedly necessary and the NST should assess readiness for discharge and develop evidence-based discharge programs to ensure that every patient discharged with HNS

receives appropriate and adequate education and training.<sup>4,5</sup> It is worth noting that the delivery skills and effects dimension of the QDTS ranked highest. This is advantageous as teaching delivery, as well as content, is important to effectively convey information and increase discharge readiness.<sup>18</sup>

As in previous studies, the overall RHDS score of patients discharged with HNS was significantly related to the content received, delivery skills and effects, and total QDTS score.<sup>18,27,30,31</sup> The QDTS score was also identified as an influencing factor for discharge readiness. These results reveal the importance of discharge education and its contribution to discharge readiness.

Previous studies have identified age, educational level, employment status, living alone, and place of residence as independent factors influencing discharge readiness.<sup>7,12,14,21,29</sup> In contrast, the present study identified expected length of HNS as the main factor influencing discharge readiness. This was probably because the access device used differed according to the expected length of HNS. For example, short-term HEN is usually delivered through a nasal feeding tube, while percutaneous endoscopic gastrostomy or jejunostomy is preferred for long-term HEN.<sup>32</sup> Obviously, the nursing aspects of percutaneous endoscopic gastrostomy/jejunostomy are more complicated than those of other methods, and this is reflected in lower RHDS scores.<sup>4</sup> Another explanation may be the heavy financial burden caused by long-term treatment, as HNS is not covered by medical insurance in China.<sup>33</sup> Additionally, RHDS scores were affected by the first-time use of HNS. It is understandable that patients receiving HNS for the first time will be new to access devices, nutrition formulas, and troubleshooting HNS-associated complications;<sup>32</sup> thus, they may have more worries about life after discharge. Length of hospital stay also influenced RHDS scores in this study. According to the steps identified by Marks, the process of discharge planning begins with the preadmission assessment and continues throughout the hospitalization period.<sup>34</sup> Thus, it is strongly suggested that HNS discharge education should be started as early as possible. Ideally, patients requiring HNS should have access to specialized NSTs at any time to consult and assist as needed.<sup>35</sup>

Another variable affecting RHDS scores in patients discharged with HNS was the NRS2002 score, which is calculated for all patients upon hospital admission to screen for malnutrition.<sup>16,36</sup> Patients at risk of malnutrition were less ready for discharge, perhaps due to disease-related malnutrition, which reduces the energy and strength required to perform self-care at home. However, those diagnosed with malnutrition had higher RHDS scores than those with digestive system malignancies. Patients with digestive system malignancies may



have additional anxieties, such as postoperative complications, side effects of adjuvant chemoradiotherapy, and possible recurrence.<sup>37,38</sup> This may affect their feelings of readiness for discharge. These findings indicate that more attention should be paid to preparing patients at risk of malnutrition and those with malignant diseases for discharge with HNS.

### ***Limitations***

This study has certain limitations. First, it was conducted in the general surgery department of a single tertiary-care teaching hospital in China and excluded patients discharged with HPN, which may restrict the generalizability of the findings. Additional multicenter studies should be conducted to examine readiness for hospital discharge in patients receiving ONS/HEN/HPN. Second, owing to time limitations, follow-up data on measures such as readmission rate, HNS adherence, and quality of life were not collected. Further studies are needed to determine the effect of readiness for discharge on the post-discharge outcomes of patients receiving HNS. Third, the study included several confounding factors. For example, patients who understood that they would receive professional support at home were not classified and analyzed separately.

### ***Conclusion***

Patients requiring HNS were moderately ready for discharge from the general surgery department. Enhancing the quality of discharge teaching may significantly improve readiness for discharge, with more attention needed for patients who have been in hospital longer, are expected to use HNS long-term, are using HNS for the first time, are at risk of malnutrition, or have a digestive system malignancy.

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### **CONFLICT OF INTEREST AND FUNDING DISCLOSURE**

The authors declare no conflict of interest.

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**Table 1.** RHDS scores (n=220)

Dimension	Total available score	Number of items	Total score	Standardized score
Personal status	20	2	14.7±3.33	7.35±1.66
Knowledge	20	2	14.5±3.48	7.26±1.74
Perceived coping ability	20	2	14.6±3.47	7.30±1.73
Expected support	20	2	14.8±3.57	7.40±1.78
Total RHDS	80	8	58.6±13.2	7.33±1.65

RHDS, Readiness for Hospital Discharge Scale  
Data are expressed as mean ± standard deviation.

**Table 2.** QDTS scores (n=220)

Dimension	Total available score	Number of items	Total score	Standardized score
Content needed	60	6	45.8±8.51	7.64±1.42
Content received	60	6	42.6±11.5	7.10±1.92
Delivery skills and effects	120	12	92.0±19.8	7.67±1.65
Total QDTS	180	18	135±28.6	7.48±1.59

QDTS, Quality of Discharge Teaching Scale  
Data are expressed as mean ± standard deviation.

**Table 3.** Difference in RHDS scores according to general information variables (n=220)

Characteristic	N (%)	RHDS standardized score	Statistic	p
Sex			T=2.81	0.005
Men	148 (67.3)	7.54±1.66		
Women	72 (32.7)	6.89±1.53		
Age			F=1.30	0.274
≤25 years	21 (9.5)	7.08±1.79		
26~55 years	131 (59.5)	7.48±1.66		
≥56 years	68 (30.9)	7.12±1.56		
Marital status			F=0.128	0.880
Married	183 (83.2)	7.33±1.57		
Single	27 (12.4)	7.24±1.86		
Other	10 (4.5)	7.55±2.43		
Educational level			H=5.24	0.387
Primary school or below	34 (15.5)	6.92±1.55		
Junior high school	48 (21.8)	7.30±1.66		
Senior high school	50 (22.7)	7.34±1.59		
Vocational degree	32 (14.5)	7.53±1.49		
College degree	50 (22.7)	7.36±1.77		
Graduate degree	6 (2.7)	8.40±2.26		
Work status			F=6.25	<0.001
Full time	123 (55.9)	7.48±1.57		
Part time	21 (9.5)	8.24±1.36		
Retired	31 (14.1)	7.21±1.56		
Unemployed	45 (20.5)	6.56±1.75		
Place of residence			T=2.13	0.035
Urban	148 (67.3)	7.49±1.64		
Rural	72 (32.7)	6.99±1.63		
Living alone			T=0.932	0.353
Yes	20 (9.1)	7.66±1.68		
No	200 (90.9)	7.30±1.64		
Access to a nearby hospital			T=0.945	0.346
Yes	199 (90.5)	7.36±1.63		
No	21 (9.5)	7.01±1.82		
Monthly income			H=10.9	0.012
≤2000 RMB	41 (18.6)	6.79±1.70		
2000~4999 RMB	71 (32.3)	7.27±1.52		
5000~9999 RMB	82 (37.3)	7.54±1.59		
≥10000 RMB	26 (11.8)	7.83±1.85		
Medical insurance coverage			T=2.94	0.004
Yes	203 (92.3)	7.42±1.59		
No	17 (7.7)	6.22±1.93		

F=one-way analysis of variance, H=Kruskal–Wallis H test, T=independent-sample t-test. RHDS, Readiness for Hospital Discharge Scale

RHDS score data are expressed as mean ± standard deviation.

**Table 4.** Difference in RHDS scores according to disease- and therapy-related information variables (n=220)

Characteristic	N (%)	RHDS standardized score	Statistic	p
Length of hospital stay			H=23.7	<0.001
<14 days	98 (44.5)	7.86±1.61		
14~28 days	84 (38.2)	7.12±1.43		
>28 days	38 (17.3)	6.41±1.72		
Number of hospitalizations			T=-0.728	0.479
1	14 (6.4)	6.89±2.36		
≥2	206 (93.6)	7.36±1.59		
Diagnosis			H=25.8	<0.001
Digestive system malignancy	24 (10.9)	7.73±1.58		
Inflammatory bowel disease	77 (35)	7.58±1.47		
Pancreatitis	42 (19.1)	7.71±1.76		
Malnutrition	11 (5)	6.82±2.42		
Intestinal obstruction	17 (7.7)	6.78±1.26		
Fistula	30 (13.6)	6.23±1.40		
Abdominal trauma	10 (4.5)	7.24±1.37		
Other	9 (4.1)	7.76±1.87		
Surgery performed			T=-0.678	0.499
Yes	150 (68.2)	7.28±1.59		
No	70 (31.8)	7.44±1.78		
Comorbidities			T=0.672	0.502
Yes	66 (30)	7.44±1.60		
No	154 (70)	7.28±1.67		
Medication at discharge			Z=-0.338	0.735
Yes	86 (39.1)	7.21±1.75		
No	134 (60.9)	7.41±1.58		
First time HNS use			Z=-3.95	<0.001
Yes	122 (55.5)	6.91±1.65		
No	98 (44.5)	7.85±1.49		
Type of HNS			F=19.7	<0.001
ONS	61 (27.7)	8.36±1.25		
HEN	126 (57.3)	6.89±1.55		
ONS+HEN	33 (15)	7.10±1.85		
Expected length of HNS			F=22.6	<0.001
<1 months	101 (45.9)	8.06±1.29		
1~6 months	107 (48.6)	6.76±1.55		
>6 months	12 (5.5)	6.26±2.49		
NRS2002 score			T=3.18	0.002
<3 points	83 (37.7)	7.77±1.51		
≥3 points	137 (62.3)	7.06±1.68		

F=one-way analysis of variance, H=Kruskal–Wallis H test, T=independent-sample t-test, Z=Mann–Whitney U test. HEN, home enteral nutrition; HNS, home nutrition support; NRS2002, Nutritional Risk Screening 2002; ONS, oral nutritional supplements; RHDS, Readiness for Hospital Discharge Scale  
RHDS score data are expressed as mean ± standard deviation

**Table 5.** Spearman's correlation coefficient between RHDS and QDTS scores (n=220)

Variable	Total QDTS	Content needed	Content received	Delivery
Total RHDS	0.620*	0.443*	0.617*	0.543*
Personal status	0.613*	0.452*	0.603*	0.543*
Knowledge	0.583*	0.407*	0.582*	0.509*
Perceived coping ability	0.588*	0.421*	0.593*	0.516*
Expected support	0.591*	0.428*	0.591*	0.515*

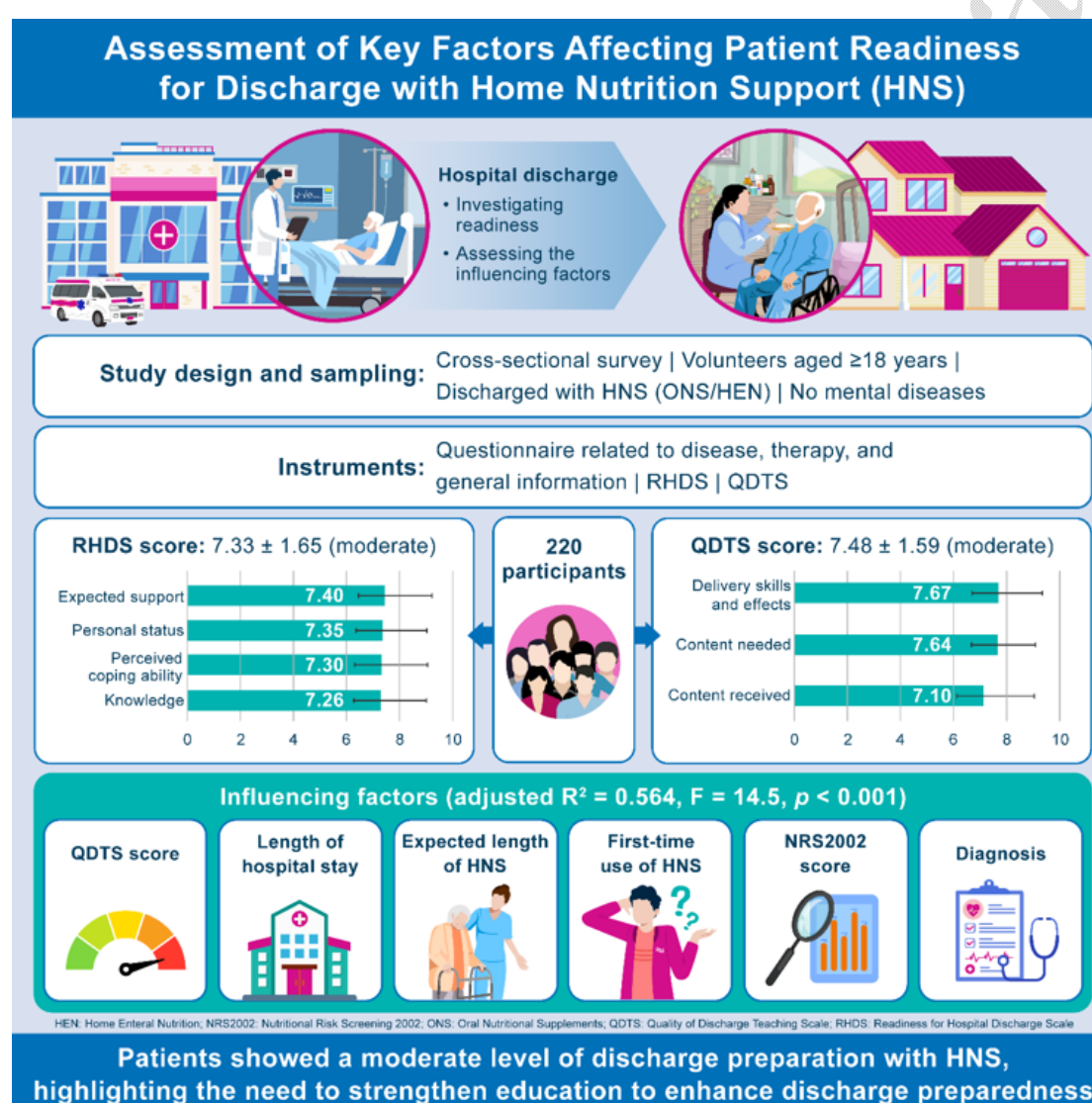
QDTS, Quality of Discharge Teaching Scale; RHDS, Readiness for Hospital Discharge Scale

\*p<0.001

**Table 6.** Multiple linear regression analysis of factors influencing RHDS scores (n=220)

Independent variable	B	SE	$\beta$	t	p	95% CI
Constant	5.80	0.862	-	6.73	<0.001	4.10~7.50
Total QDTS score	0.456	0.051	0.440	8.87	<0.001	0.355~0.588
Length of hospital stay	-0.313	0.116	-0.141	-2.70	0.008	-0.543~-0.084
Expected length of HNS	-0.868	0.203	-0.312	-4.27	<0.001	-1.27~-0.467
First time HNS use	0.780	0.201	0.236	3.89	<0.001	0.384~1.18
NRS2002 score	-0.577	0.181	-0.170	-3.18	0.002	-0.934~-0.219
Diagnosis						
Malnutrition (ref. digestive system malignancy)	1.01	0.505	0.134	2.00	0.047	0.015~2.01

CI, confidence interval; HNS, home nutrition support; NRS2002, Nutritional Risk Screening 2002; QDTS, Quality of Discharge Teaching Scale; RHDS, Readiness for Hospital Discharge Scale  
 $F=14.5$ ,  $p<0.001$ ;  $R^2=0.606$ , adjusted  $R^2=0.564$



**Graphical abstract.**