BPR MCS
Bulletin of Pioneering Researches of Medical and Clinical Science

Bulletin of Pioneering Researches of Medical and Clinical Science

Available online: https://bprmcs.com
2025 | Volume 4 | Issue 2 | Page: 1-6

Impact of Intervention on Treatment Outcomes and Referral Rates in Hepatitis C Patients

Marta Torrens[1*], Darcy Bowman[2], Eberhard Schatz[3]

[1] Addiction Research Group, Hospital del Mar Medical Research Institute, Barcelona, Spain.
[2] Public Affairs, Gilead Sciences Ltd, London, UK.
[3] Correlation European Harm Reduction Network, Amsterdam, The Netherlands.

Abstract

This study aimed to evaluate the impact of implementing critical value management combined with push short messaging service (SMS) on enhancing the referral rates of patients testing positive for hepatitis C antibody (anti-HCV). Patients with positive anti-HCV results between January 1, 2015, and October 31, 2021, did not receive any specific intervention. From November 1, 2021, to July 31, 2022, patients who tested positive were notified through critical value management and push SMS. For hospitalized patients, a qualified physician coordinated with an infectious disease specialist for consultation, whereas outpatients were directed to visit the liver disease clinic. Statistical analyses, including the chi-square correlation test, one-sided two-proportion test, and linear regression, were conducted to assess the association between the intervention and referral outcomes. Among 638,308 individuals tested for anti-HCV, 5,983 were positive. Of the referred patients, 51.8% were aged 18–59 years, while 10.8% were ≥ 75 years old. The chi-square correlation test indicated a significant association between the intervention and referral rate ($P = .0000$, $P < .05$). A one-sided two-proportion test comparing pre (p_1) and post-intervention (p_2) referral rates yielded significant results using normal approximation and Fisher's exact test ($P = 0.000$, $P < .05$), supporting the hypothesis that $p_1 - p_2 < 0$. Linear regression analysis produced the equation: referral = 0.1396 × intervention + 0.3743 ($P = 8.79e{-}09$, $P < .05$), confirming a significant effect of the intervention with a coefficient of 0.1396. The combined strategies of critical value management and push SMS were significantly associated with referral rates among patients with positive anti-HCV results.

Keywords: Critical value, Patients with hepatitis C, Effectiveness validation, SMS, Referral rate

Corresponding author: Marta Torrens
E-mail: marta.giner@uni-muenster.de

Received: 19 April 2025
Revised: 07 June 2025
Accepted: 09 June 2025

How to Cite This Article: Torrens M, Bowman D, Schatz E. Impact of Intervention on Treatment Outcomes and Referral Rates in Hepatitis C Patients. Bull Pioneer Res Med Clin Sci. 2025;4(2):1-6. https://doi.org/10.51847/gZuPWuJMYu

Background

Hepatitis C continues to be a significant contributor to chronic liver disease. In 2015, around 71 million people worldwide were infected with HCV [1], but only a fifth were diagnosed, and fewer than 10% received treatment [2]. The global effort to eliminate HCV heavily depends on identifying and managing cases in high-prevalence countries such as China, Egypt, India, and Pakistan [3]; however, diagnosis rates in these regions remain below 25% [4]. In China, the introduction of direct-acting antiviral (DAA) therapies has revolutionized treatment, achieving sustained virological response rates exceeding 90% [5]. Despite these advances, timely detection and referral remain essential to control the disease effectively. Currently, a high rate of false-negative results, combined with low referral and treatment uptake, hampers HCV

management, and many healthcare providers are insufficiently aware of the importance of screening and treatment. Even when in-hospital screening identifies patients with positive anti-HCV results, a large proportion do not follow up with infectious disease specialists [6]. Given the high potential for cure and low awareness levels, interventions that improve patient engagement and referral are critical. This study implemented measures, including push notifications via SMS, essential alerts of value, and rapid reporting of positive results to enhance referral rates. Analysis comparing outcomes before and after the intervention revealed that these strategies significantly increased referrals for patients testing positive for anti-HCV, providing a practical model for enhancing hospital-based hepatitis C management.

Materials and Methods

Study population

A retrospective, single-center, cohort-controlled design was employed at China-Japan Friendship Hospital. The study encompassed all patients who underwent anti-HCV testing between January 1, 2015, and July 31, 2022. Data retrieved from the Hospital Laboratory Information System (LIS) included patient demographics, contact information, anti-HCV test results, and HCV-RNA status. The intervention targeted individuals with positive anti-HCV results who had not received HCV-RNA testing within the hospital. Routine preoperative screening identified patients undergoing surgical procedures. Patients already referred to specialists were excluded. The primary objective was to ensure that antibody-positive patients without prior specialist follow-up were referred to the infectious disease department for evaluation and treatment.

Inclusion criteria

- Patients were tested for anti-HCV at the hospital during the study period.
- Positive anti-HCV result.
- Complete data available.

Exclusion criteria

- Samples sent from external hospitals.
- Duplicate test results.
- Missing or incomplete information.

The study was approved by the Ethics Committee of China-Japan Friendship Hospital (2020YFC2004803) and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

Laboratory procedures

Anti-HCV detection

Testing for anti-HCV antibodies was performed using kits from Shenzhen YHLO Biotechnology Co., Ltd., China, stored at 2–8 °C. All assays were run on the fully automated YHLO iFLASH3000 chemiluminescence analyzer.

HCV-RNA measurement

HCV-RNA quantification utilized the nucleic acid test kit provided by Sun Yat-sen University Daan Gene Co., Ltd., China, with reagents kept at −20 °C. Nucleic acid extraction and purification were conducted using room-temperature reagents from the same manufacturer. Extraction was carried out on the Daan Smart32 instrument, followed by amplification and detection with the Roche COBAS480 system.

Study methods

Intervention procedures

For outpatients, two intervention approaches were applied starting November 1, 2021. First, patients with positive anti-HCV results were notified through the hospital's SMS platform. The message read: "Hello, your hepatitis C antibody test at China-Japan Friendship Hospital is abnormal. We recommend visiting the liver disease clinic for further evaluation and treatment. [China-Japan Friendship Hospital 84205976]." Second, the positive result was highlighted with an upward arrow ('↑') in the test report, and patients were verbally advised to consult the Infectious Disease Department for further assessment. For inpatients, positive anti-HCV results were first flagged to the attending physician via a pop-up alert in the hospital information system (HIS) and simultaneously sent as an SMS notification. Physicians were prompted to review the patient's HCV-RNA status, and if the HCV-RNA test was positive, consultation with an infectious disease specialist was required. The medical office team monitored HCV-RNA results for all patients who were antibody-positive. If the responsible physician had not requested a consultation, the staff contacted the doctor to ensure a consultation application was submitted. This established a closed-loop workflow encompassing screening, notification, monitoring, and feedback, ensuring patients were successfully referred and improving overall referral rates.

Data from January 1, 2015, to October 30, 2021, were collected without any intervention, whereas data from November 1, 2021, to July 31, 2022, included the SMS and critical value interventions.

Definitions

Patient referral

Outpatients were promptly seen at the Infectious Disease or Hepatology Departments, while inpatients were

consulted promptly by these departments and referred as needed [6].

Consultation/Referral rate

Referral rate was calculated as:

Number of anti-HCV-positive patients in specialty or consultation/number of anti-HCV-positive patients in the same period × 100% [7].

Statistical analysis

Key Study variables

Variables included patient gender, age, intervention status, referral status, diagnosis, and whether HCV-RNA turned negative.

Data handling

Age was recorded in years, with patients younger than one month coded as 0 years. Any record with missing data for one or more key variables was excluded from analysis.

Statistical methods

Levene's test and two-sample t-tests were applied for comparisons of numerical variables. Categorical variables were analyzed using chi-square tests to assess associations. Differences in referral rates between groups were evaluated with a one-sided two-proportion (z) test [8]. Linear regression was used to examine relationships between variables and quantify the effect size. Statistical significance was set at $\alpha = 0.05$.

Analytical tools

Data collection and organization were performed in Microsoft Excel 2017 (Redmond, WA). Statistical analysis was conducted using Python 3.10 within Jupyter Notebook and Minitab 21.1 (licensed version).

Results

From 2015 to July 31, 2022, a total of 638,308 patients were screened for anti-HCV at our hospital, of whom 5,983 tested positive. Detailed data are presented in **Table 1 and Figure 1**.

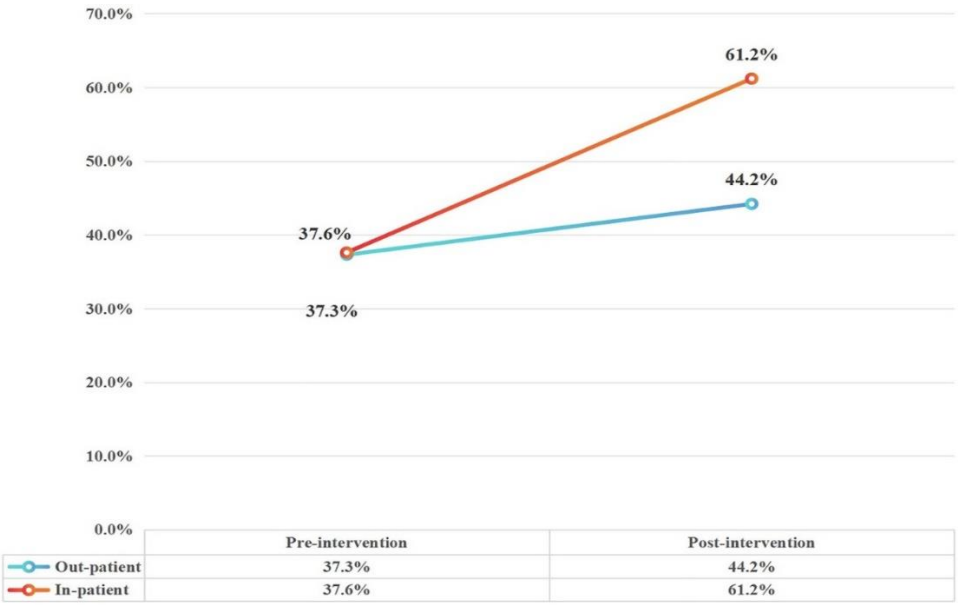

Figure 1. A total of 638,308 cases were tested for anti-HCV at our hospital

Table 1. Basic data

Items		Pre-intervention	Post-intervention
Anti-HCV	Negative	556,880	81,428
	Positive	5552	431
Anti-HCV (+)	Outpatient	2926	248
	Inpatient	2626	183
Referral rate	Outpatient	37.30%	44.20%
	Inpatient	37.60%	61.20%
Gender	Male	2588	210
	Female	2954	221
Referred		2078	221
Referral patient HCV-RNA (+) person-time (proportion)		447 (21.5%)	46 (20.8%)
Not referred		3474	210
Reported		40	40

Patients were categorized into pre-intervention and post-intervention groups. To assess whether the variance in age was similar between the groups, Levene's test was performed, yielding a statistic of 2.7663 with a P-value of 0.0963. As this P-value exceeded 0.05, no significant difference in age variance was observed between the two groups. Subsequently, a two-sample t-test assuming equal variances was conducted, resulting in a t-statistic of 1.6956 and a P-value of 0.0900. This confirmed that there was no statistically significant difference in age between patients in the pre- and post-intervention groups. Among the referred patients, 51.8% were aged 18–59 years, while 10.8% were 75 years or older.

The relationship between gender and intervention status was also examined. Male and female distributions were visually compared between the pre- and post-intervention groups, as illustrated in **Figure 2**, which suggested similar proportions. Chi-square correlation analysis produced a value of 0.517 with a P-value of 0.4710. Since the P-value exceeded 0.05, it indicated that patient gender was not significantly associated with whether they received the intervention.

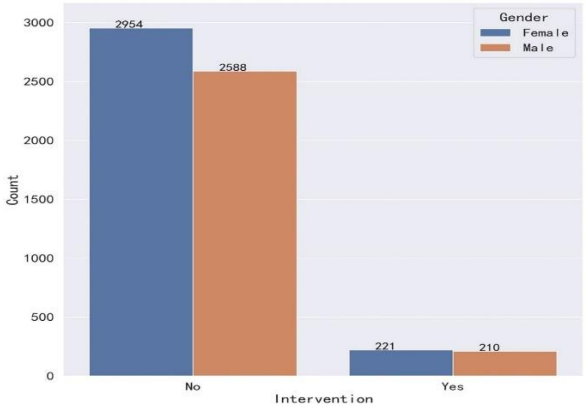

Figure 2. Gender association with the intervention

Patients were categorized into pre-intervention and post-intervention groups. A chi-square test was conducted to examine the relationship between the intervention and referral outcomes, yielding a P-value of 0.0000. Because this value is below the 0.05 threshold, it indicates a statistically significant association between the intervention and referrals. The referral rate increased from 0.3743 in the pre-intervention group to 0.5139 in the post-intervention group, demonstrating a notable improvement following the intervention and suggesting that the intervention effectively enhanced referral rates **(Table 2)**.

Table 2. Referral is correlated with intervention using the chi-square test

	Pre-intervention	Post-intervention	Total
Not referred	3474 3418.0	210 266	3684
Referred	2078 2134.0	222 166.02	2300
Missed	69	4	[a]
Chi-square test Pearson = 33.015; P-value = .000; P < .05 Likelihood ratio = 32.127; P-value = .000; P < .05			

[a] The "missed" column reflects cases with incomplete basic data; these entries were not analyzed as they do not contribute meaningful information.

To determine whether the referral rates differed between the pre- and post-intervention groups, a one-sided test for two proportions was performed. Both the normal approximation and Fisher's exact test produced values of 0.000 (P < .05), supporting the alternative hypothesis that the referral rate increased after the intervention (p_1-$p_2 < 0$).

As shown in **Table 3**, the post-intervention group exhibited a substantially higher referral rate compared with the pre-intervention group, demonstrating that the intervention had a significant positive effect on promoting referrals among patients with positive anti-HCV results (see Supplemental Materials).

Table 3. Two-ratio test of pre-intervention and post-intervention referral rates

	N	Event	Sample *p*
Pre-intervention	5552	2078	0.374
Post-intervention	432	222	0.514
Method p_1: pre-intervention referral rate p_2: post-intervention referral rate Difference = $p_1 - p_2$ Test Original hypothesis: H_0: $p_1 - p_2 = 0$			

Alternative hypotheses: H_1: $p_1 - p_2 < 0$		
Method	*Z*	P
Normal approximation	−5.60	.000
Fisher's exact test		.000
P < .05		

Discussion

The World Health Organization (WHO) has set a goal for hepatitis C elimination, aiming for 30% of infected individuals to be aware of their infection status by 2020, and for 50% of eligible patients to receive treatment and achieve sustained virologic response (SVR) [9]. In China, approximately 10 million people live with chronic hepatitis C, representing 14% of the global burden, while around 2.5 million individuals urgently require antiviral therapy but remain unaware of their infection [10]. Multiple factors influence the low referral rate for hepatitis C in China. Many patients lack awareness about hepatitis C or the significance of a positive anti-HCV result, often believing that treatment is unnecessary in the absence of symptoms or that the disease is incurable. Furthermore, the highly specialized structure of hospital departments can make it challenging for patients to identify the appropriate clinical pathway, and non-specialist clinicians may not prioritize hepatitis C management.

Micro-elimination strategies, which divide national elimination targets into smaller, manageable goals for specific subpopulations, provide a practical means to deliver treatment and preventive interventions more efficiently [11]. Targeted anti-HCV screening for patients undergoing invasive procedures, such as surgeries or endoscopies, facilitates the early identification of positive cases and enables timely, standardized treatment—provided there is an effective referral mechanism in place. To enhance referral rates at our hospital, outpatients with positive anti-HCV results were notified via push SMS, which included information about the relevant department and contact numbers for consultation. This approach provided patients with more precise guidance on where and how to seek follow-up care, improving compliance and continuity of treatment. For inpatients, critical value alerts were generated through the HIS system to notify qualified physicians, prompting timely HCV-RNA testing and ongoing monitoring of treatment status. Additionally, SMS notifications were sent to these physicians to ensure they received patient test results promptly, representing a practical solution to enhance clinical follow-up.

A dedicated "hepatitis C special" program was established within the hospital, coordinated across multiple departments including the Information Department, Infectious Diseases, and Clinical Laboratory. This program involved designing patient screening, diagnosis, referral, treatment, and follow-up procedures, supervising their implementation, and managing data collection, analysis, and feedback. Educational materials were also distributed in dental clinics and physical examination centers to encourage patients to proactively undergo hepatitis C screening, facilitating early detection, referral, and treatment.

Following these interventions, the referral rate among patients with positive anti-HCV antibodies increased from 37% to 51%. Specifically, outpatient referral rates rose from 37.3% to 44.2%, and inpatient referral rates increased from 37.6% to 61.2%. Daily monitoring of anti-HCV and HCV-RNA test results through the LIS system allowed the medical department to verify whether clinicians had issued appropriate HCV-RNA tests and referral recommendations through the HIS system, ensuring effective supervision of clinical referrals.

The hospital's "small-scale clearance" strategy [11, 12] demonstrated that combining critical value alerts with push SMS notifications could effectively encourage physicians to initiate necessary referral actions and inform patients about the significance and procedures of follow-up care. This approach is simple, practical, and replicable in other hospital settings. Notably, the reporting rate of hepatitis C increased dramatically from 9% before the intervention to 89% after implementation, indicating that including positive anti-HCV results in critical value management raised physician awareness and significantly improved patient referral outcomes.

There are several limitations in this research. The intervention did not lead to a significant improvement in outpatient referral rates, likely because no follow-up phone calls were made after sending SMS notifications. It is possible that patients did not notice the messages or failed to seek care, or that some patients visited other hospitals, which were not captured in our data. Supporting this, hospital records indicate that some patients bypassed initial screening at our facility and directly came for HCV-RNA testing and treatment. Future interventions will include telephone follow-ups to enhance outpatient referral compliance.

Additionally, this study was conducted at a single center with a relatively short intervention period and limited data. The retrospective, non-randomized design is another limitation. Our focus was primarily on facilitating the successful referral of anti-HCV-positive patients to liver disease clinics for early, standardized antiviral therapy, and we did not collect information regarding patients' underlying conditions, such as existing liver damage.

Conclusions

In conclusion, the approval of multiple direct-acting antivirals (DAAs) in China, coupled with the inclusion of some medications under medical insurance, has gradually reduced the cost of hepatitis C treatment, creating an unprecedented opportunity for elimination. However, the disease's asymptomatic nature and long course result in many carriers remaining undiagnosed [13]. The intervention described here offers a simple and effective method for achieving successful referrals, enabling early diagnosis and timely, standardized antiviral treatment. Such strategies contribute directly to the global goal of eliminating viral hepatitis by 2030 [14].

Acknowledgments: None.

Conflict of interest: None.

Financial support: None.

Ethics statement: None.

References

1. The Polaris Observatory HCV Collaborators. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. Lancet Gastroenterol Hepatol. 2017;2(3):161–76.
2. World Health Organization. WHO global hepatitis report 2017. Geneva: World Health Organization; 2017 [cited 2020 Mar 2]. Available from: http://www.who.int/hepatitis/publications/global-hepatitis-report2017/en/
3. Gower E, Estes C, Blach S, Razavi-Shearer K, Razavi H. Global epidemiology and genotype distribution of the hepatitis C virus infection. J Hepatol. 2014;61(1 Suppl):S45–57.
4. CDA Foundation. Polaris observatory. Washington (DC): CDA Foundation; 2019 [cited 2020 Mar 2]. Available from: http://cdafound.org/polaris/
5. Rao HY, Duan ZP, Wang GQ, Wei L, Jia JD, Li J, et al. Key update points of the guidelines for prevention and treatment of hepatitis C (2019 edition). Zhonghua Gan Zang Bing Za Zhi. 2020;28(2):129–32.
6. Health and Family Planning Commission of the People's Republic of China. Hepatitis C virus screening and management. Beijing: Health and Family Planning Commission of the People's Republic of China; 2014.
7. China United Liver Health Promotion Center, Hepatology Society of Chinese Medical Association, Laboratory Medicine Society of Chinese Medical Association, Chinese Society of Infectious Diseases, Chinese Preventive Medicine Association, et al. Management process of hepatitis C in-hospital screening in China (trial). Chin J Clin Hepatol. 2021;37(7):1534–9.
8. Hu LP. How to correctly use the Z-test: two rate comparison general difference Z-test and SAS realization. Si Chuan Jing Shen Wei Sheng. 2020;33(5):431–5.
9. World Health Organization. Regional action plan for viral hepatitis 2016–2020. Geneva: World Health Organization; 2015.
10. World Health Organization. Up to 10 million people in China could die from chronic hepatitis by 2030—urgent action needed to bring an end to the "silent epidemic" [Internet]. Geneva: World Health Organization; 2019 [updated 2016 Jul 26; cited 2020 Sep 3]. Available from: https://www.who.int/china/news/detail/26-07-2016-up-to-10-million-people-in-china-could-die-from-chronic-hepatitis-by-2030-urgent-action-needed-to-bring-an-end-to-the-silent-epidemic-
11. Lazarus JV, Wiktor S, Colombo M, Thursz M. Micro-elimination: A path to global elimination of hepatitis C. J Hepatol. 2017;67(4):665–6.
12. Feng B, Zhang J, Wei L. Inadequate awareness of hepatitis C among non-specialist physicians in China. Adv Med Educ Pract. 2011;2:209–14.
13. Ren TQ, Li LM, Yang QQ, Zhang J, Xu Y, Chen Y, et al. Economic analysis and strategy of hepatitis C screening. Chin J Clin Hepatol. 2020;36(10):2305–9.
14. World Health Organization. Global health sector strategy on viral hepatitis 2016–2021. Geneva: World Health Organization; 2016 [cited 2020 Mar 2]. Available from: https://www.who.int/hepatitis/strategy 2016 - 2021/ghss-hep/en/