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Brief Report

Advanced liver fibrosis and care continuum in emergency department patients with chronic hepatitis C

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ABSTRACT

Background: FIB-4, a non-invasive serum fibrosis index (which includes age, ALT, AST, and platelet count), is frequently available during ED visits. Our objective was to define 1-year HCV-related care outcomes of ED patients with known HCV, for the overall group, and both those with and without advanced fibrosis.

Methods: As part of an ongoing HCV linkage-to-care (LTC) program, HCV-infected ED patients were identified retrospectively via medical record review. Components of FIB-4 were abstracted, and patients with an FIB-4 > 3.25 were classified with advanced fibrosis and characterized with regards to downstream HCV care continuum outcomes at one-year after enrollment.

Results: Of the 113 patients with known HCV, 38 (33.6%) had advanced fibrosis. One-year outcomes along the HCV care continuum after ED encounter for 'all' 113, 75 'without advanced fibrosis', and 38 'advanced fibrosis' patients, respectively, were as follows: agreeing to be linked to care [106 (93.8%), 72 (96.0%), 34 (89.5%)]; LTC [38 (33.6%), 21 (28.0%), 17 (44.7%)]; treatment initiation among those linked [16 (42.1%), 9 (42.9%), 7 (41.2%)]; sustained virologic response 4 weeks post-treatment among those treated [15 (93.8%), 9 (100.0%), 6 (85.7%)]; documented all-cause mortality [10 (8.8%), 3 (4.0%), 7 (18.4%)]. Notably, 70% of those who died had advanced fibrosis. For those with advanced liver fibrosis, all-cause mortality was significantly higher, than those without (18.4% versus 4.0%, $p = 0.030$).

Conclusions: Over one-third of HCV-infected ED patients have advanced liver fibrosis, incomplete LTC, and higher mortality, suggesting this readily-available FIB-4 might be used to prioritize LTC services for those with advanced fibrosis.

1. Background

The Centers for Disease Control and Prevention (CDC) estimates that 2.3–3.7 million Americans are living with chronic hepatitis C virus (HCV) [1]. Among individuals chronically infected with HCV, without effective treatment, up to 7% will die from liver cirrhosis or hepatocellular carcinoma, typically occurring after 20 to 30 years of progressive liver fibrosis [2]. Furthermore, in recent years, HCV-related mortality has surpassed the total number of deaths from 59 other nationally notifiable infectious conditions combined which includes human immunodeficiency virus (HIV) [3].

The burden of HCV infection in emergency department (ED) patients is significant because EDs serve as a medical safety net for many Americans, who are also at high risk for HCV. Several seroprevalence studies conducted in urban EDs have reported extremely high prevalence of HCV antibodies, ranging from 13 to 18% [4-7]; many of these patients remain unaware of their HCV serostatus, and/or their virologic status. Additional data highlighting the burden of HCV among ED patients comes from a 10-year healthcare utilization survey (2001−2010) which estimated approximately three-quarter million HCV-related ED visits [8]. The disease burden and clinical challenge associated with delivering testing and linkage-to-care (LTC) services in the episodic care environment of the ED is significant. Numerous experts have reported that the limited capacity of specialty care services to take new patients across the nation, represents a major public health challenge [7,9,10]. For individual patients, the impact is manifested by long back logs of wait times for in-take appointments (>6 months), and frequent failures to LTC after the ED encounter [11]. Ultimately, these lead to suboptimal outcomes along the HCV care continuum for the ED HCV-infected population, which have particularly important adverse implications for those with advanced stage liver disease [12].

Up until now, the EDs role in addressing the clinical and public health challenges of untreated HCV has focused exclusively on

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identifying those who are infected, and offering referral for LTC. Considering the fact that limited resources exist for LTC services for ED patients who have chronic HCV, a new paradigm is required, which prioritizes LTC and treatment services for those in greatest need of prompt HCV care; such an approach could represent a significant improvement over the existing standard of care (non-prioritized LTC services routinely offered out of EDs currently across the US). The simple non-invasive liver fibrosis serum index, FIB-4 [13], which combines age with commonly-available laboratory values [(platelets, alanine aminotransferase (ALT), aspartate aminotransferase (AST))], has been validated for estimating liver fibrosis stage and could provide a simple pragmatic risk stratification tool to help prioritize HCV LTC processes.

Our primary aim was to determine the outcomes of the downstream HCV care continuum among ED patients with known chronic HCV infection, one year after standard of care (i.e. non-prioritized) HCV LTC services were provided. Our secondary aim was to determine if those with advanced liver fibrosis (retrospectively estimated using the non-invasive FIB-4 index) was associated with inadequate downstream care continuum outcomes.

2. Methods

The study site is the urban adult XXX Hospital ED (XXXED) with approximately 70,000 annual visits. The ED serves a predominantly socioeconomically disadvantaged population with high risk for HCV infection. A seroprevalence study estimated approximately 8% of patients in this ED had chronic HCV infection [7]. This study was conducted as a quality improvement evaluation of an ED-based HCV LTC program with approval from The XXX University School of Medicine Institutional Review Board.

From March 10, 2015 to November 17, 2015, a pilot HCV LTC program was initiated. Potentially eligible participants for the program were ED patients with chronic HCV infection, defined as having a positive HCV RNA in the electronic medical record (EMR). Dedicated paid staff who were trained as patient care navigators by RER (Emergency Medicine) and RI (Infectious Diseases), approached those patients determined to have chronic HCV, and offered them expedited LTC appointments at The XXX Viral Hepatitis Clinic (XXVHC). If the patient was interested in being linked, the ED patient navigators contacted case managers from the XXVHC who either came directly down to the ED to meet the patient (if the patient was in the ED during XXVHC operation hours) or contacted the patient by phone the next business day (if the patient was in the ED during non-business hours) to arrange an expedited LTC appointment. Patient demographics and blood laboratory test values within 6 months of the encounter date, including ALT, AST, and platelet count, were obtained from the EMR from the ED visit. FIB-4 scores were calculated using the following formula:

$$\text{FIB}-4 = \frac{\text{Age (years)} \times \text{AST (U/L)}}{\text{Platelet count}\left(10^9/\text{L}\right) \times [\text{ALT (U/L)}]^{1/2}}$$

FIB-4 scores were calculated and then mapped to a F0–F4 equivalent scale [14]. In using FIB-4, a score of >3.25 is characterized as F3–F4, or advanced liver fibrosis. One year after each patient's original encounter date, a retrospective chart review was carried out to determine HCV-related clinical information, including LTC status, liver fibrosis staging by ultrasound-based transient elastography (FibroScan) [15], fibrosis staging biomarker test (FibroSure) [16], or other modalities, initiation of HCV antiviral treatment, sustained viral response 4 weeks post-treatment (SVR4), as well as reported mortality. SVR4 was used to serve as an initial measure of treatment success instead of SVR12, a definite measure for virologic cure at 12 weeks post-treatment [17-19], given the anticipated challenges with follow-up from this urban ED population, and the pilot nature of this study. SVR4 is considered an acceptable initial measure of treatment success in HCV clinical trials [17-19]. The equivalent of transient elastography to advanced fibrosis (F3–F4) is a value greater than or equal to 9.5 kPa [20]. Mortality documented on EMR was further categorized, as likely liver-related or not based on the final diagnosis and the physician notes of the evaluating infectious diseases specialist, who is also the medical director of the JHVHC (co-author MSS).

Chi-squared tests or Fisher exact tests for categorical data and *t*-test for continuous data were performed to determine differences in prevalence of advanced liver fibrosis by socio-demographic status using SAS 9.4 (SAS Institute Inc., Cary, North Carolina). All-cause mortality in 1000 person-years among patients with known chronic HCV infection one year after enrollment were calculated and compared to a group of randomly selected, 1:1 ratio, age-, sex-, race-matched ED patients. The dataset used for the comparison group was, for feasibility and convenience purposes, was taken from an identity-unlinked blood-borne pathogen seroprevalence study carried out around the same time as this study between December 2015 and January 2016. The identity-unlinked seroprevalence study was approved by The XXX University School of Medicine Institutional Review Board.

3. Results

During the 8-month study period, a total of 114 ED patients with anti-HCV antibodies and HCV RNA (or documented clinical viral hepatitis C diagnosis) were approached by patient care navigators. The majority of patients were male (62.3%), African American (79.0%), and aged 50 years and older (71.9%). Twenty-six (22.8%) patients were co-infected with HIV. Among 114 patients identified as being HCV RNA positive, 113 (99.1%) had sufficient data collected as part of routine medical care practice to allow calculation of an FIB-4 score and were included for further analysis (Table 1). Median and mean FIB-4 scores were 2.26 (IQR: 1.41 to 4.68) and 4.62 (SD: 12.27). There were 38 (33.6%) patients with FIB-4 score > 3.25 (i.e. advanced fibrosis). Comparing those with FIB-4 > 3.25 and ≤ 3.25, there were no differences with regard to sex, race, or HIV status. However, as expected, those with FIB-4 > 3.25 were significantly older than those with lower scores (FIB-4 > 3.25: 57.2 ± 7.5 years, FIB-4 ≤ 3.25: 52.6 ± 10.0 years, $p = 0.013$).

Table 1
Characteristics of 113 patients with chronic hepatitis C viral infection by FIB-4 index in an urban emergency department

Characteristics	Total population *n* (%)	FIB-4 ≤ 3.25 *n* (%)	FIB-4 > 3.25 *n* (%)
Total number	113	75	38
Age (years)*			
18–44	15 (8.8)	12 (16.0)	3 (7.9)
45–54	44 (38.9)	34 (45.3)	10 (26.3)
55–64	41 (36.3)	21 (28.0)	20 (52.6)
≥65	13 (11.5)	8 (10.7)	5 (13.2)
Gender			
Male	70 (61.9)	45 (60.0)	25 (65.8)
Female	43 (38.1)	30 (40.0)	13 (34.2)
Race			
Black	89 (78.8)	61 (81.3)	28 (73.7)
White	20 (17.7)	12 (16.0)	8 (21.0)
Declined	4 (3.5)	2 (2.7)	2 (5.3)
HIV Status			
HIV +	25 (22.1)	14 (18.7)	11 (28.9)
HIV −	88 (77.9)	61 (81.3)	27 (71.1)
Linkage to care			
Agreed to linkage	106 (93.8)	72 (96.0)	34 (89.5)
Attended 1st appointment	38 (33.6)	21 (28.0)	17 (44.7)
Treatment initiated	16 (14.2)	9 (12.0)	7 (18.4)
Sustained viral suppression	15 (13.3)	9 (12.0)	6 (15.8)
Deceased within 1 year after the initial encounter†			
Yes	10 (8.8)	3 (4.0)	7 (18.4)

* $p = 0.047$.
† $p = 0.030$ (Fisher's exact test).

We examined varied steps along the HCV care continuum as follows: "Agree to Linkage", "Linked to Care", "Liver Fibrosis Staging", "Treatment – Initiated", and "Sustained Virologic Response, SVR4". Outcomes of the care continuum were evaluated for the overall group of patients (n = 113), as well as for those with advanced liver disease (n = 38) categorized by FIB-4, and those without advanced liver disease (n = 75). For the overall group of patients (see Fig. 1), 106 (93.8%) patients agreed to be linked to HCV care in the ED; 38 (33.6%) made their first scheduled appointment at the JHVHC; 36 (31.9%) had liver fibrosis staging; 16 (14.2%) initiated HCV antiviral treatment within 1 year; 15 (13.3%), including 3 patients who did not complete treatment course, had a non-detectable viral load after the treatment and had sustained virologic response at least four weeks (SVR4) after the completion of treatment course. For the group of 38 patients with advanced liver fibrosis (see Fig. 1), 34 (89.5%) patients agreed to be linked to HCV care in the ED; 17 (44.7%) made their first scheduled appointment at the JHVHC; 8 (21.1%) had transient elastography for liver fibrosis staging; 7 (18.4%) initiated HCV antiviral treatment within 1 year; 6 (15.8%) completed an antiviral treatment regimen; 6 (15.8%) had a non-detectable viral load after the treatment and had sustained virologic response at least four weeks (SVR4) after the completion of treatment course. For the group of 75 patients without advanced liver fibrosis (see Fig. 1), 72 (96.0%) patients agreed to be linked to HCV care in the ED; 21 (28.0%) made their first scheduled appointment at the JHVHC; 19 (25.3%) had transient elastography for liver fibrosis staging; 9 (12.0%) initiated HCV antiviral treatment within 1 year; 6 (8.0%) completed an antiviral treatment regimen; 9 (12.0%), including 3 patients who did not complete treatment course, had a non-detectable viral load after the treatment and had sustained virologic response at least four weeks (SVR4) after the completion of treatment course.

Among the 22 patients who were linked to care but did not receive HCV treatment within one year of ED encounter [which included 10 (45.5%) with advanced fibrosis], six were lost follow-up [1 advanced fibrosis], six had HCV antiviral treatment deferred due to severe comorbid diseases [all advanced fibrosis; three deceased; two within one year of ED encounter; 1 due to liver disease], four were denied HCV antiviral treatment by insurers due to absent or mild fibrosis (F0 or F1) [0 advanced fibrosis], four received antiviral treatment one year after the ED encounter [2 advanced fibrosis; including one who did not fill the antiviral prescription and was lost follow-up], one moved to another state [1 advanced fibrosis], and one was observed to have self-cleared (i.e. undetectable viral load without treatment) [0 advanced fibrosis].

At one year post-enrollment date, at least 10/113 (8.8%) patients were deceased [[i.e. mortality: 88.5 per 1000 person years (PYs)] identified from the medical chart]. 67 patients were confirmed still alive by chart review, and the remaining 36 had no data in the medical chart available to ascertain whether they were alive or deceased. Of those who died, four (40%) were likely due to liver-related complications of which all had advanced liver fibrosis and three were not treated. Advanced liver fibrosis defined by FIB-4 index was significantly associated with all-cause mortality (p = 0.030) (Table 1). In comparison, among 113 age-, sex-, race-matched control ED patients who did not have HCV infection, 3 died within one year after their ED encounter, [i.e. mortality: 26.5 per 1000 PYs, mortality rate ratio for HCV positive vs negative: 3.33 (95%CI: 0.94, 11.79)].

Regarding ED obtained FIB-4 scores, characterization of liver fibrosis staging in this group of patients by imaging was as follows. Among 27 patients in whom we obtained transient elastography results, 8 (29.6%) had advanced fibrosis by imaging, and 19 did not. Of those 8 patients 6/8 (75%) had FIB-4 scores > 3.25. Of those remaining 19 patients without advanced fibrosis, 15/19 (79%) had FIB-4 scores ≤ 3.25.

4. Discussion

In this study, among persons with chronic hepatitis C attending an urban ED, we found a high prevalence of patients with advanced liver disease using a non-invasive blood-based serum fibrosis index that was available to the providers during the ED visit for this group of patients. That finding coupled with the demonstrated incomplete high rates of linkage to curative care services and very high mortality among those with advanced liver disease, suggests that liver disease staging at the time of the ED visit could be used to prioritize LTC services for patients in the ED. Multiple factors including loss to follow-up, patient deference of treatment due to comorbidities, and treatment denial by the insurer were some of the key determinants for the majority of patients who were linked to care but did not receive HCV treatment, in spite of the fact that HCV is now a curable infection. These findings underscore the importance of the need to improve systems for linking ED patients with chronic hepatitis C into care, to include using readily available risk of progression information and education to help prioritize what are now scarce resources for achieving HCV cures for those patients with advanced liver fibrosis.

To the best of our knowledge, this is one of the first ED LTC programs for previously diagnosed HCV-infected patients in the nation. In an ED where we have a prevalence of chronic HCV of 12% (which equals to several thousand individual ED patients per year, in just a single ED), significant gains could be realized by advancing efforts to better link those with previously diagnosed HCV, including initiation of antiviral treatment, clearing HCV, and reducing the pool of HCV in the community. Finding from our ED compare favorably to composite reported

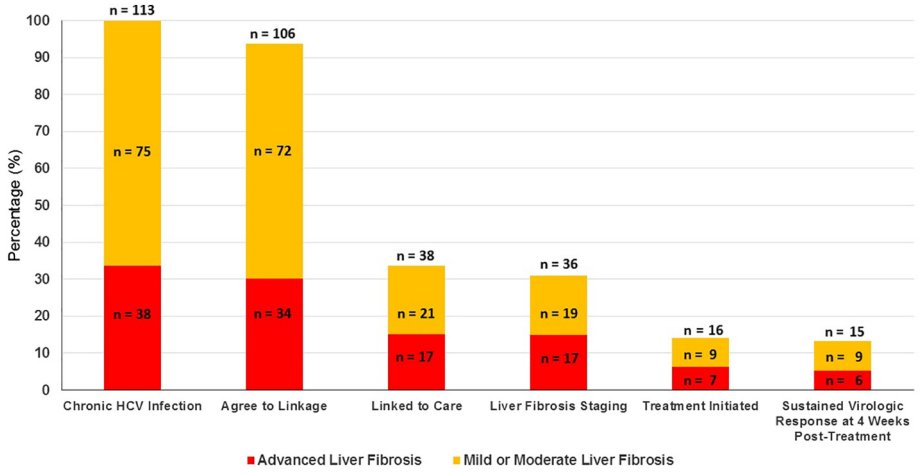

Fig. 1. HCV care continuum in 113 chronic HCV-infected emergency department patients by advanced liver fibrosis status which was estimated by FIB-4 index. Footnote: 1 ED patient was excluded from the final analysis due to incomplete data, leaving n = 113.

outcomes from two other U.S. urban ED HCV screening programs [12], with: higher rates of interest in LTC services (94% versus 52%); similar actual LTC rates (34% versus 32%); slightly higher rate of treatment initiation (14% versus 8%); and double the rates of sustained viral response, SVR4 (12% versus 6%).

A major gap in the HCV care continuum observed in this group of patients is attendance at an initial LTC visit, which we believe could be directly related to shortfalls in the current approaches being used for communicating both the urgency and necessity of receiving HCV care – from both the patient and the downstream provider/system perspectives. Patients might have limited knowledge or misconception regarding HCV, due to a variety of factors including the slow and indolent nature of the disease, lingering perceptions of the lack of effective treatment options (rooted in communities historical experience with interferon therapy), and perceptions of HCV having a relatively low morbidity and mortality (relative to other infectious disease condition such as HIV). To mitigate these challenges, we are proposing use of a simple risk stratification tool which could be deployed in real-time in the ED and reliably predict clinical outcomes at the time of the ED encounter (such as FIB-4 or point-of-care transient elastography). Implementation of such as tool could represent a paradigm shift in that it would provide critical information to both patients and providers (as well as systems) and potentially impact the timeliness of engagement in care, and other key steps along the HCV care continuum.

The current nationwide shortage of an adequate specialist workforce for caring and treating for the almost 3 million Americans with chronic HCV infection [21], is recognized to contribute to national trends of long wait time for patients with chronic HCV infection, to be first seen by a trained specialist. Although this is not the case at our institution, the issue of under-capacity for HCV care is particularly palpable for patients and providers who work in urban ED settings, where the burden of disease is especially high. The median wait time reported from EDs in Oakland, California and Birmingham, Alabama was at least 5 months [12]. Despite the relatively small number of patients evaluated in this pilot study (and the fact that we work in a system where HCV specialty care exists 'in house'), our preliminary findings highlight the potential adverse impact of delayed HCV care among those with advanced fibrosis; <50% of those linked to care; only 41% of those linked receiving treatment within 1 year; 60% of those linked have treatment deferred, due to comorbidity and/or severe liver diseases (50% of them deceased). Integration of an FIB-4 calculator into the EMR and incorporating that tool into the routine process of patient care for those with chronic HCV infection is a feasible approach and would permit rapid assessment of fibrosis severity. Similar approaches has been demonstrated in the ED setting for patients in need of other 'risk stratified services' such as palliative care, with favorable outcomes [22,23]. Downstream outcomes for those with untreated HCV could be significant, given current published LTC rates (~32%) for HCV-infected patients identified in the ED [12]. The integration of a rapid, non-invasive index such as the FIB-4 could allow for the assessment and prioritization of patients with advanced fibrosis for connection to resources and LTC while they are still receiving care in the ED. Thus, LTC rate among ED HCV-infected patients will be significantly improved as well as the downstream stages of the HCV Care Continuum.

In the determination of fibrosis severity, the liver biopsy is traditionally considered the "gold standard". Non-invasive tests, however, are a more suitable alternative for monitoring disease progression and are not subject to sampling error and intra/inter-observer variability [24]. Among non-invasive tests, transient elastography (FibroScan) has been used to obtain a liver stiffness measurement. A simpler and cheaper alternative, the FIB-4 index was advanced about a decade ago, and advocated for use based on reliability as well as wide-spread availability using values from a patient's comprehensive metabolic panel [13,14]. Consistent with the findings in the literature [25-27], the FIB-4 index measurements here were highly correlated with FibroScan results and correctly identified patients with advanced fibrosis in our ED. Notably, in our state Maryland, even though Medicaid provides HCV antiviral treatment coverage to participants with the fibrosis stage of F2 or higher that is determined by liver elastography (FibroScan®) or the commercially available blood index known as HCV FibroSure™ [28], we suggest that FIB-4 would provide a highly practical tool that can be used to prioritize initial referral for services, and once linked to care, additional staging tests could be performed as required for approval of initiation of medical treatment.

Our prevalence of advanced fibrosis (34%) was similar to that observed in another cohort of patients in care for chronic hepatitis C drawn from patients who had medical care provided in one of 4 large integrated healthcare systems in U.S. [14], but was much higher than the 13% with chronic HCV infection, which reported in the general U.S. population [29]. Notably, our all-cause mortality rate was approximately 2.5 to 4 times higher than that reported by two cohorts of chronic HCV-infected individuals [14,30], and 10 times higher than that in the general U.S. population [31]. Furthermore, relative to our general ED population, the all-cause mortality rate was 3.3 times higher for those with previously diagnosed HCV infection, matching for age, sex and race. Opportunities for interventions along each stage of the HCV care continuum including linkage to care, initiation of antiviral treatment, adherence to treatment, would most likely decrease both the HCV-related, and all-cause mortality.

Generalizability is the most significant limitation of our study. Our long-standing ED-based HIV program made it easier for the staff in our ED to adapt to the HCV LTC process with the affiliated viral hepatitis clinic. It is possible that our successful LTC might not be reproducible in other resource-limited EDs, such as in the low-income rural setting or a setting which lacks nearby and engaged partners for LTC. In addition, this study was limited by the data available in the EMR. For example, when the FIB-4 was calculated, the values which were drawn from the EMR included current (and if not available), as well as most recent up to the six months prior to date of the encounter. It is possible that these values, such as platelet count, AST, and ALT, could have changed during this time. Additionally, chart review one-year after the index visit, may not have provided a comprehensive picture of the patient's HCV care continuum measures, as patient information may not be fully captured based on their encounters within our health system; however the vast majority of patients who visit the JHHED use our health system as their primary care site. Moreover, selection bias may have occurred such that the patients we studied may not be fully representative of all those with chronic HCV in the ED - we enrolled a convenience sample including only those for whom the patient-care navigator was present. We estimated that up to 4500 unique ED patients could have chronic HCV infection during the 8-month study period or approximately 1000 patients with chronic HCV infection, were a full-time linkage to care staff was in place (and were every HCV infected patient been previously tested with documentation of their results in the chart) [7]. Of note, many of those individuals would not able to be included in the program due to varied factors including but not limited to lack of documentation of their current serostatus, high acuity of illness and/or altered mental status during their ED stay, in addition to the lack of 24/7 availability of LTC staff. Nevertheless, this is a small convenience sample, we found that there was no significant difference with regard to age, gender, and race between enrollees and those who had chronic HCV infection using data from the 2013 seroprevalence study conducted in the same ED [7]. Another limitation of this study is that we used SVR4 instead of SVR12 to measure the treatment success for patients who received HCV treatment, given the anticipated challenges with follow-up from an urban ED population. However, the bias is likely limited since the extremely high concordance between SVR4 and SVR12 with a positive predictive value of 98% and a negative predictive value of 100% [19]. Finally, HCV medication for those who did not have advanced liver fibrosis (F0 – F2) by the standard staging method was limited in our state since they were not eligible for treatment by the State of Maryland Medicaid guidelines.

In summary, we found a high prevalence of advanced liver fibrosis as measured by FIB-4 index, as well as a high mortality rate among patients with chronic HCV infection in our ED. Given the substantial burden of HCV-related illness in urban ED patients nationally, and the recognized fact that EDs are the often the only point of contact with the health care system for many of these patients, we propose incorporating FIB-4 based rapid assessment into ED-based HCV screening and LTC programs in order to prioritize LTC for patients with advanced liver fibrosis, as well as routine ED clinical practice. Increasing both provider and patient awareness of the value of liver fibrosis staging could also serve to motivate patients with advanced liver disease to attend scheduled LTC services and yield improvements in downstream HCV care continuum outcomes.

Contributors

Y-HH designed the study. DS, AVP, VV, and MSS had primary responsibility for the data collection. Y-HH performed data analyses. YH-H, DS, RER, RI, MSS, and DLT primarily interpreted results. YH-H, AVP, and VV primarily drafted the manuscript. RER, MS, RI, MSS, and DLT performed critical editing of the manuscript.

Declaration of interests

We declare no competing interests.

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Ethics committee approval

A quality improvement evaluation of an ED-based HCV LTC program received an approval from The Johns Hopkins University School of Medicine Institutional Review Board. The Johns Hopkins University School of Medicine Institutional Review Board approved the identity-unlinked seroprevalence study.

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