Epidemiology
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Regional and Temporal Variations in the Prevalence of HCV among Hemodialysis Patients in Saudi Arabia

Mohamed Shoukri[1,3], Mohamed Al Sebayel[2,3], Faisal Abaalkhail[2], Hany Elbeshbeshy[2], Mohamed Abdelfatah[2], Waleed Al-Hamoudi[4], Ahmed Elgohary[4], Abdelrahman Housawi[4], Futwan Al-Mohanna[4] and Hussien Elsiesy[2,3*]

[1]Department of Cell Biology, KFSHRC, Saudi Arabia
[2]Organ Transplant Center, KFSHRC, Saudi Arabia
[3]Al-Faisal University College of Medicine, Riyadh, Saudi Arabia
[4]Department of Gastroenterology, King Saud University

Abstract

Hepatitis C infection among Hemodialysis (HD) patients is a recognized global problem. The incidence and prevalence of HCV in dialysis patients vary widely among geographical regions in the Kingdom of Saudi Arabia (KSA). However, the HCV incidence has marked decline in all regions within KSA. But it is noted that the risk of occasional nosocomial transmission remains. We intend to apply the Seemingly Unrelated Regression (SUR) models to develop a scientific strategy to estimate the future burden of HCV in dialysis units. These predictions may provide baseline information for disease management intervention and cost control. The model based predictions show that the decline in the HCV incidence which started in 2004 is projected to potentially reach zero by the year 2014.

Keywords: Hepatitis C infection; Regional variations; Seemingly unrelated regression; Prediction analysis; Models goodness of fit

Introduction

Infection with the hepatitis C virus (HCV) is the leading cause of chronic liver disease worldwide. With an estimated prevalence of 3% in the world population (around 170 million infected individuals), HCV heavily burdens public health [1]. An estimated 2-3% of the world's population is living with hepatitis C virus (HCV) infection, and each year, >350000 die of HCV-related conditions, including cirrhosis and liver cancer. The epidemiology and burden of HCV infection varies throughout the world, with country-specific prevalence ranging from <1% to >10%. In contrast to the United States and other developed countries, HCV transmission in developing countries frequently results from exposure to infected blood in healthcare and community settings [1]. The World Health Organization (WHO) releases global estimates on the prevalence and burden of HCV infection [2].

Hepatitis C virus (HCV) infection is a significant problem in the management of hemodialysis patients. A high prevalence of HCV infection in hemodialysis patients has been reported. Risk factors such as the number of blood transfusions or duration on hemodialysis have been implicated.

Several studies documented that HCV infection is more common in dialysis patients than in healthy populations. The best data regarding prevalence among dialysis patients were provided by Dialysis Outcomes and Practice Patterns Study (DOPPS), which was a prospective, observational study that reported the prevalence of HCV among adult hemodialysis patients randomly selected from 308 representative dialysis facilities in France, Germany, Italy, Japan, Spain, the United Kingdom, and the United States [2]. The overall prevalence was 13.5% (compared with global prevalence in the general population of approximately 3%).

Several reports have documented the progressive increase in the prevalence of HCV among dialysis patients, in both Western and developing countries. A study in Syria reported that the overall prevalence of anti-HCV among HD patients was 48.9%; 24.4% in one center (Al-Mouassat Hospital) and 88.6% in the other (Kidney Hospital). It is interesting to see that there was a significant correlation between prevalence of anti-HCV and duration of HD. The prevalence was 36.7% for patients on HD for <3 years and 65% in patients on HD for >3 years (p < 0.05) [3].

Megmar et al. [4] reported that the HCV infection has declined in regions where the screening for anti-HCV in blood banks and hemodialysis-specific infection control measures were adopted. In Brazil, these measures were implemented in 1993 and 1996, respectively. Analysis of risk factors showed that length of time on hemodialysis, blood transfusion before screening for anti-HCV and treatment in multiple units were statistically associated with anti-HCV (p < 0.05) [5]. Studies by Espinosa et al. [6] and Natov et al. [7] showed a significant decline of hepatitis C infection in hemodialysis patients of Central Brazil, ratifying the importance of public health strategies for control and prevention of hepatitis C in the hemodialysis units. In addition, HCV infected hemodialysis patients have an increased risk of death when compared with those not infected [8].

Another study was conducted in Libya whose aim was to investigate the incidence and prevalence of HBV and HCV infection in the HD population, as well as risk factors for infection. All adult patients receiving maintenance HD (n = 2382) in Libyan dialysis centers (n = 39) were studied between May 2009 and October 2010. Patients who were seronegative for HBV and HCV (n = 1160) were followed up for 1 year to detect seroconversions. The prevalence of HBV ± HCV infection varied widely between HD centers from 0% to 75.9%. Wide variation in rates of newly acquired infections was observed between dialysis centers [9]. It is clear then that patients on maintenance HD in Libya have a high incidence and prevalence of HCV infection. The

factors associated with HBV and HCV infection are highly suggestive of nosocomial transmission within HD units.

This paper has two objectives. Firstly; focusing on data from the Kingdom of Saudi Arabia, we quantify the regional and temporal variability in both the number of patients on hemodialysis (HD), and predict the number of HCV cases among them. Secondly; we use statistical prediction models to explore the pattern of increase (decrease) in the number of patients needing dialysis, and use these predictions to estimate the future count of HCV among HD patients. We summarize the results by constructing an overall confidence limits on the perceived population prevalence, and focus on the regional variation in the prevalence of HCV among HD patients in Saudi Arabia. We develop a Seemingly Unrelated Regression (SUR) models to investigate regional and temporal variation in the prevalence of HCV among Saudi HD patients.

Methods

From the above studies we conclude that the main risk factors implicated for HCV infection among HD patients are:

The number of blood transfusions

The prevalence of anti-HCV antibodies increases with the number of units of blood products [5]. The risk of acquiring post transfusion HCV infection has declined. In one study, the risk was < 1 per 3000 units of blood products transfused [6]. Among hemodialysis patients, the decreased risk is due to both the screening of blood products for anti-HCV antibodies and to the decreased use of blood transfusion to treat anemia.

Dialysis vintage

The risk of seroconversion increases with time on dialysis. The interval since beginning dialysis has been reported to be significantly longer among anti-HCV-positive patients, compared with anti-HCV-negative patients, and the risk of HCV infection increases considerably after a decade of hemodialysis [10].

Mode of dialysis

Patients on peritoneal dialysis are at lower risk for HCV infection, compared with hemodialysis patients [7,10,11]. In a group of 129 anti-HCV-negative patients on chronic dialysis, for example, the rate of seroconversion was 0.15 per patient-year on hemodialysis, compared with 0.03 per patient-year on continuous ambulatory peritoneal dialysis (CAPD) [12]. In contrast to hemodialysis patients, the duration of peritoneal dialysis does not appear to be a risk factor for acquiring HCV infection [13,14]. Consistent with this observation are the findings from one Israeli study, in which, compared with peritoneal dialysis patients, the prevalence of HCV infection was higher among hemodialysis patients, and HCV-infected patients were treated longer than non-infected patients [13]. The majority of anti-HCV-positive CAPD patients may have acquired HCV infection while on hemodialysis

The prevalence of HCV infection in dialysis patients is quite variable. Several studies have been conducted in Saudi dialysis units. The data presented in (Table 1) support this claim. Summarizing the data we find that the prevalence is between 30% and 80%. This table is adapted from [14] and the references therein [15-32].

Data from the studies presented in Table 1, displayed in Figure 1, may be used to construct and overall 95% confidence interval on the HCV prevalence in dialysis units. This is given as (0.308, 0.810). This

(ID) Author, Year	# HD patients	% HCV patients and 95% CI
Ayoola et al. [18]	74	42 (31-53)
Hussein et al. [19]	67	40 (28-52)
Huraib et al. [20]	1147	68 (65-71)
Ahmad et al. [21]	92	82 (74-90)
Souqiyh et al. [28]	1392	70 (68-72)
Al-Muhanna [23]	125	43 (34-52)
Alshohaibet.al. [24]	139	52 (44-60)
Bernieh et al. [25]	94	60 (50-70)
Shaheen et al. [26]	408	72 (68-76)
Omer et al. [27]	149	85 (79-91)
Soyannwo et al. [28]	97	51 (41-61)
Kumar [32]	47	51 (37-65)
Souqiyyeh etal. [33]	6694	50 (40-60)
Saxena et al. [34]	189	44 (73-51)
Al-Jiffri er al. [35]	248	73 (67-70)
Kashem et al. [30]	90	47 (37-57)
Almawi et al. [22]	115	15 (8-22)
Karkar et al. [31]	265	29 (24-34)

Table 1: Adapted from Karkar [10]. HCV among HD patients in selected 18 studies.
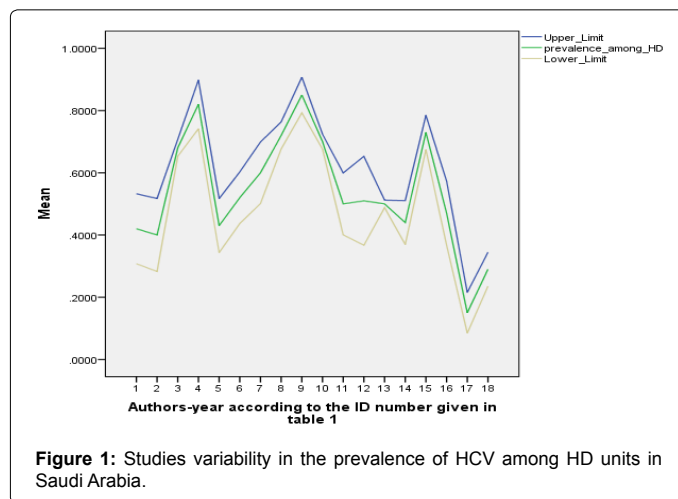

Figure 1: Studies variability in the prevalence of HCV among HD units in Saudi Arabia.

interval overlaps with the worldwide interval prevalence as reported in [10] (Figure 1).

The Saudi data for the regional distribution of HCV among dialysis patients was obtained from the prospectively collected data by the Saudi Center for Organ Transplant that is reported yearly as SCOT annual report [32]. The database divides the transplant centers into five regions; central region (Riyadh & Qassim), western region (Jeddah and Makkah), eastern region (Dammam and Al-Khobar), northern region, and southern region. The number of HD patients and the count of HCV infected among them were reported for each region for the years 1999-2011. These data will be used to train our prediction model, while data for the years 2012, 2013, and 2014 will be used for model validation. Figure 2 depicts the regional distribution of the HCV in dialysis patients over the period 1999-2011.

Results

Our prediction tool utilizes two equations with dependent variables (HD and HCV) that we consider as a group because they bear a close conceptual relationship to one another. Aside from this conceptual

relationship, the two linear regression models have, outwardly, no connection with one another (Figure 2). Each equation models a different dependent variable and the independent variables in each equation need not be the same Zellner [33]. The two equations are:

$$HD = \beta_{01} + \beta_{11} \, Region + \beta_{21} \, Year + \in_1$$

$$HCV = \beta_{02} + \beta_{12} \, Region + \beta_{22} \, Year + \in_2$$

As can be seen from the above set-up the two equations appear unrelated, and we might be tempted to estimate the regression parameters independently, but in fact they are not. For this reason the system is referred to as a system of Seemingly Unrelated Regression (SUR) models. Of course, if the two equations actually are un-related, then we should estimate them separately. But it may be the case that there is a relation between the equations, brought forward by correlation between the two error terms. If the two error terms are correlated, then we can gain a more efficient estimator by estimating the two equations jointly, as was shown by Zellner [33]. If $\in_1$ is correlated with $\in_2$, then knowledge of $\in_2$ can help us predict the value of $\in_1$ efficiently. The estimation of these models is achieved quite easily using the Procedure "SYSLIN", implemented in the SAS program [34].

Coding the independent variables:

Code year = Year -1999 +1

$$X_1 = \begin{bmatrix} 1 & \text{if Riyadh} - \text{Qassim} \\ 0 & \text{else} \end{bmatrix}$$

$$X_2 = \begin{bmatrix} 1 & \text{if Jedda} - \text{Mekka} \\ 0 & \text{else} \end{bmatrix}$$

$$X_3 = \begin{bmatrix} 1 & \text{if Eastern Province} \\ 0 & \text{else} \end{bmatrix}$$

$$X_4 = \begin{bmatrix} 1 & \text{if Southern region} \\ 0 & \text{else} \end{bmatrix}$$

The Northern region is obtained when all the X's are set to zero. The regression equations from the SUR are given as:

HD = -49.08 + 1624.77(X_1) + 2530.31 (X_2) +350.54 (X_3) + 767.62 (X_4) + 102.13 (code year) (1)

$R^2 = 0.949$.

HCV = 227.35 + 611.15 (X_1) + 1135.9 (X_2) +61.5 (X_3) + 403.7 (X_4) -8.73 (code year) (2)

$R^2 = 0.966$.

We produced predictions based on models (10) and (2) in Table 2. We use the concordance correlation coefficient introduced by Lin [35] as a measure of agreements between two sets of measurements, to assess the goodness of fit (GOF) of the prediction model. High agreement between the observed and the model based predicted counts would be an indicative of the reproducibility of the model. The measure of agreement is given by:

$$\rho_c = \frac{2 r s_o s_p}{s_o^2 + s_p^2 + \left(\mu_o - \mu_p \right)^2}$$

where r is the Pearson's correlation between the observed and the model-based predicted counts, (μ_o, μ_p) are the means of the observed and the model-based predicted counts, while (s_o, s_p) are their corresponding
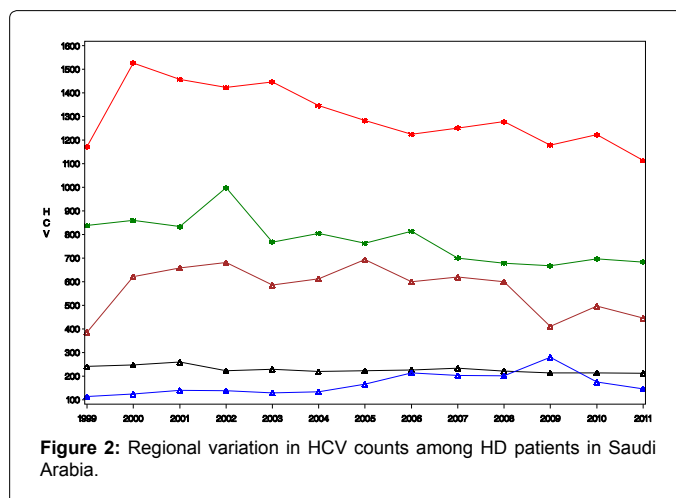

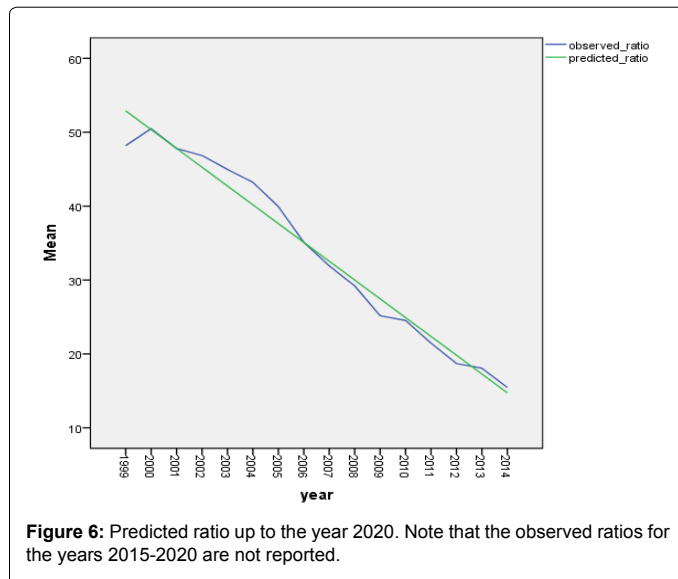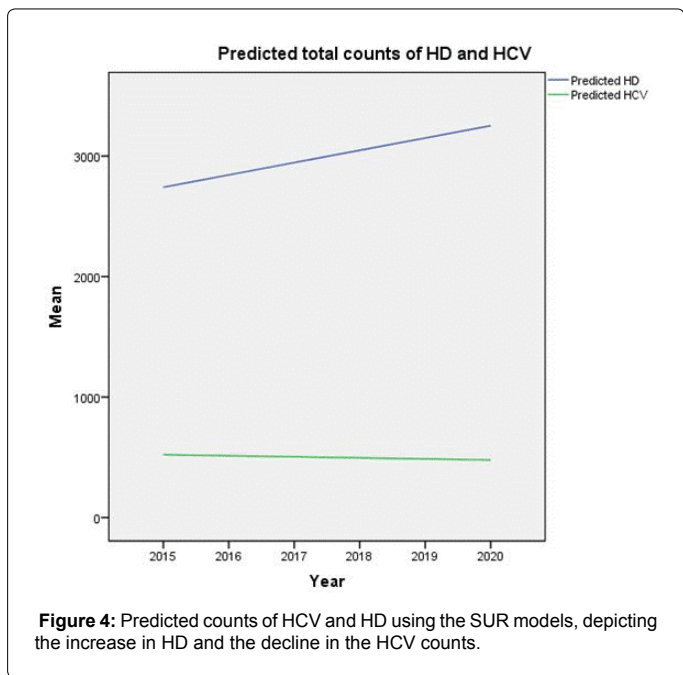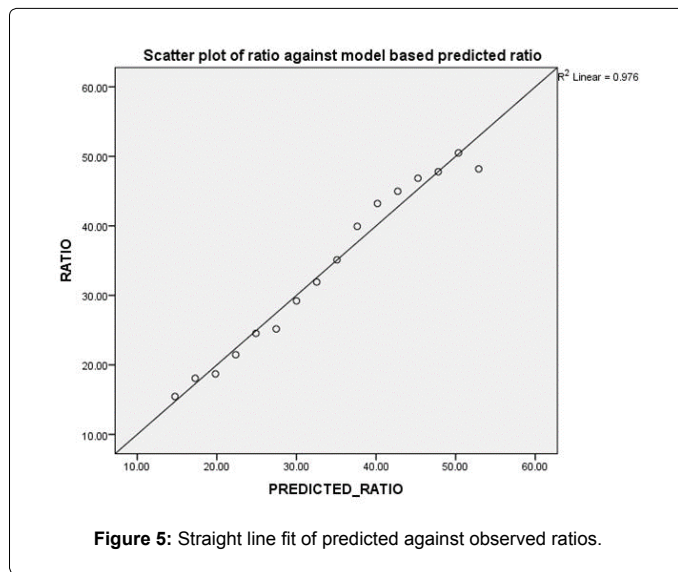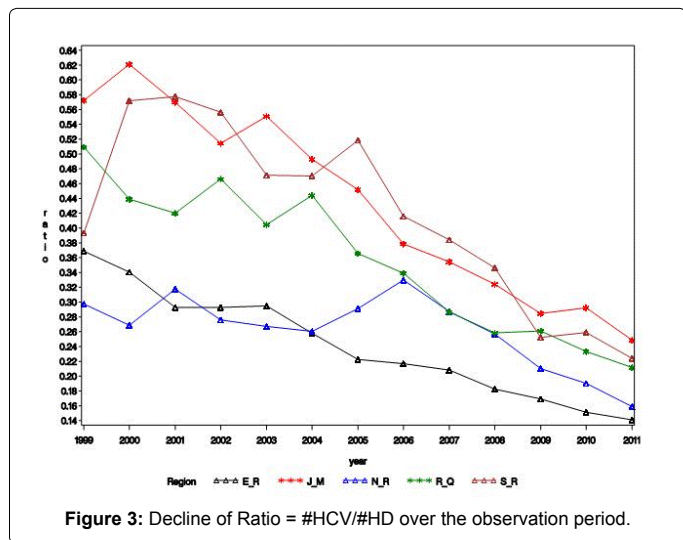**Figure 2:** Regional variation in HCV counts among HD patients in Saudi Arabia.

Parameter	Observed #HD	Predicted #HD	Observed # HCV	Predicted # HCV
Mean (μ)	1720	1720	608	608
Standard deviation (s)	1027	1000	424	417
Pearson's Corr.(r)	-0.974		-0.983	
Concordance Corr.ρ_c	0.974		0.982	

Table 2: Summary statistics to test the model goodness of fit (Internal validity).

Year	Region	Predicted HD	Predicted HCV
2012	Riyadh-Qassim	3006	716
2012	Jedda-Makka	3911	1241
2012	Eastern	1731	167
2012	Southern	2148	509
2012	Northern	1381	105
2013	Riyadh-Qassim	3108	707
2013	Jedda-Makka	4013	1232
2013	Eastern	1833	158
2013	Southern	2250	500
2013	Northern	1482	96
2014	Riyadh-Qassim	3210	698
2014	Jedda-Makka	4115	1223
2014	Eastern	1935	149
2014	Southern	2352	491
2014	Northern	1585	88

Table 3: Model validation, validating data, 2012-2014.

standard deviations. Note that r = ρ_c when $\mu_o = \mu_p$, and $s_o = s_p$. Note that the sign of ρ_c, is the same as the sign of Pearson's correlation coefficient. Close value of ρ_c to ± 1, indicate higher agreement among the observed and the predicted counts. From the summary statistics in Table 2, it can be seen that the models produced predicted counts that are in close agreement to the observed counts. We can also validate the model by comparing the observed counts in the validation set in the years (2012-2014) with the predicted counts based on the SUR model in equations (1) and (2) (Table 3). For the HD counts, the concordance correlation between the observed counts in the years 2012-2014, and the model based predictions is $\rho_c = 0.997$, and for the HCV the corresponding concordance between the predicted counts and the observed counts is $\rho_c = 0.995$.

Figure 3: Decline of Ratio = #HCV/#HD over the observation period.

Figure 5: Straight line fit of predicted against observed ratios.

Figure 4: Predicted counts of HCV and HD using the SUR models, depicting the increase in HD and the decline in the HCV counts.

Figure 6: Predicted ratio up to the year 2020. Note that the observed ratios for the years 2015-2020 are not reported.

Predicting the burden of HCV among dialysis patients: Ratio prediction

Alternative to the predictions models of counts, we may be interested in predicting the percentage of HCV patients among the dialysis patients. Figure 3 shows that the rate of decline of this ratio # HCV/# HD across the 5 regions is almost the same (Figures 3-5).

Figure 5 shows that the linear relationship between the predicted ratio and the observed ratios. The concordance correlation $\rho_c = 0.988$ indicating the excellent goodness of fit of the model to the data, and its high predictability. In Figure 6 we show the models based decline in the predictions of the future ratios.

Predicted ratio = 55.44 – 2.544 X year code.

Discussion

We have documented the significant variation in the rate of HCV

in dialysis units among the regions in Saudi Arabia. We noted also that, starting from the year 2004, there has been a steady decline in this incidence in all regions. This decline coincides with the worldwide trend, and is attributed to the improved infection control practices, screening for blood products, and the strict adherence to universal hygiene precautions. Assuming that the infection control practices in Saudi Arabia will remain in place, we predict, based on the regression models introduced here, that the prevalence of HCV in dialysis units would be near zero by the year 2019.

There are two limitations to our study; firstly potential risk factors such as gender, age, and HBV or HIV infections were not investigated. Secondly; our study is ecological meaning that the analyses used retrospective information from a national surveillance system of registration. Therefore, we should cautiously interpret the results, and one should not be tempted to extend these findings to risk prediction at the individual subject level.

Conflict of interest

The Authors declare that there is no conflict of interest regarding the publication

of this article.

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