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Risk factors from HBV infection among blood donors: A systematic review

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ABSTRACT

Objective: To perform a systematic review of the scientific literature to identify risk factors associated with hepatitis B viruses (HBV) infection among blood donors.

Methods: The literature search was carried out on PubMed and Scopus databases using the keywords "risk factors" "HBV infection" and "blood donors". No date or language restrictions were applied to the search. This literature review was completed in March 2014. The selection process and the reporting of the review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement. The Newcastle Ottawa scale was using to evaluate the quality of each single primary study.

Results: Out of 172 records resulted in the search, 5 papers were included in the final analysis because they are within acceptance criteria. Two of the selected studies were cross-sectional and three of them were case-control studies. Significant association resulted with some demographic and behavioral risk factors, such as marital status, dental treatment/procedure history, no stable relationship or multiple partners and family history of HBV infection.

Conclusions: The systematic review performed encourages to conduct further research among blood donors in order to fully understand risk factors among donors in more extensive thus to provide valuable information about surveillance.

1. Introduction

Blood transfusion is a life-saving intervention that has an essential role in patient management within health care systems [1]. Unfortunately, blood transfusion is not without risks and may lead to the transmissions of infectious agents from donor to recipient including hepatitis C virus (HCV), human immunodeficiency virus (HIV), syphilis–causing *Treponema pallidum* and hepatitis B virus (HBV) [2]. Many cases of HBV infections in adult populations were found to be associated with blood transfusions, since HBV is infective through blood and body-fluid, including vertical transmission [3].

The hepatitis B surface antigen (HBsAg) in serum is the first seromarker to indicate active HBV infection, either acute or chronic [4]. Since 1982 there was available an hepatitis B vaccine, highly effective in the prevention of HBV transmission [3], with a consequence of a remarkable reduction in the prevalence and incidence of HBV infection.

Despite this, the World Health Organization (WHO) has estimated that there are still 360 million chronically HBV infected people and 5.7 million HBV-related cases worldwide, spread with a high variability across the countries (*e.g.* in the difference between low and high income countries) [5]. It has been estimated that infections with HBV was responsible for about 59% of hepatocellular carcinoma cases in developing countries [6].

Overall, the majority of the world population lives in areas of moderate (2%–7%) to high endemicity (> 8%) for chronic HBV infection [defined as dual seropositivity for HBsAg and for antibodies against hepatitis B core antigen (anti-HBc)] [7].

Screening of donated blood for transfusion-transmissible infections represents one of the most important strategy for blood transfusion safety and availability, and the presence of this type of infection among blood donors is a rare event. Up to now, no review has been conducted studying systematically the risk factors associated with chronic HBV infection among blood donors; so, the objective of the present study is to perform a systematic review of the scientific literature with the specific aim to identify such risk factors associated with chronic HBV.

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2. Materials and methods

2.1. Search strategy

A medical literature review was carried out on Medline (PubMed) and Scopus databases using the keywords "risk factors" "HBV infection" and "blood donors". We performed searches for: "risk factors" AND "HBV infection" AND "blood donors". No date or language restrictions were applied to the search.

When duplicate or repeated publications were encountered in the databases search, the papers, when eligible, were considered only once. This literature review was completed in March 2014.

2.2. Article selection

We selected all studies evaluating the risk factors from HBV infection among blood donors. The selection and the reporting of the review were performed according to the Preferred Reporting Items Systematic Reviews and Meta-Analyses Statement [8], in order to provide univocal and comparable data as shown in the flow-chart (Figure 1).

Preliminary, two authors independently assessed the study selection of potentially relevant titles and abstract, based on the established criteria. Subsequently, when there was some doubt, the full text was found and read. In a final phase, disagreements between authors were resolved by consensus.

Articles were excluded if (1) studies were not pertaining to the topic "risk factors from HBV infection among blood donors"; (2) there was no reported odds ratio (OR) resulted from univariate analysis or adjusted odds ratio (AOR) resulted from multivariate logistic analysis for identifying risk factors associated with HBV infection among blood donors; (3) the full text was not available; (4) language was not in English, Italian or Spanish; (5) article was a letter or an editorial or a previous review.

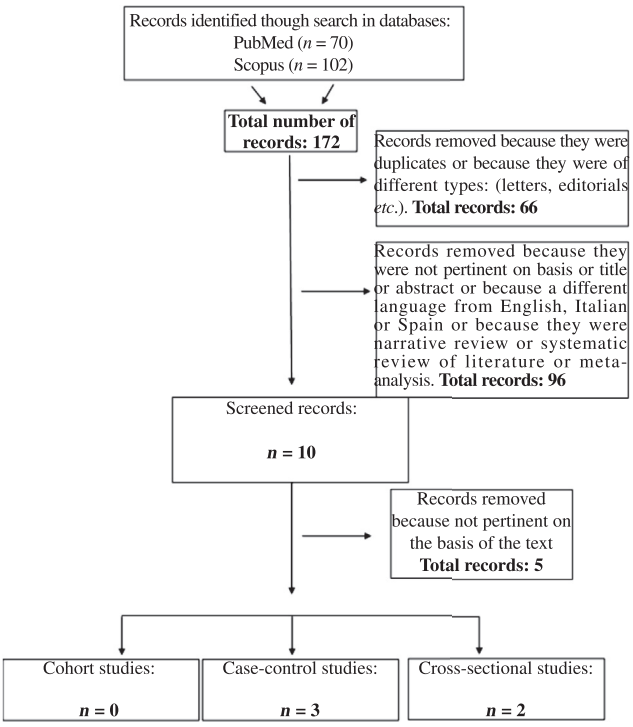

Figure 1. Flow chart of the selection studies of the systematic review.

2.3. Data extraction and quality assessment

All publications were analyzed by both investigators, who independently reviewed the papers to identify relevant information and to extract data. Disagreements were resolved by consensus.

The Newcastle Ottawa scale for case-control studies was performed [9], and the adapted form of the Newcastle Ottawa cohort scale for cross-sectional studies were used to evaluate the quality of the studies [10]. Disagreements were resolved by consensus.

3. Results

Out of the 172 references identified in the initial search, 162 were removed because they were duplicates or because they were of different types: (letters, editorials, *etc*.) or because they aligned with the study objectives or because they were in language different from English, Italian and Spanish. After the abstract selection, 10 full-text were evaluated. Of these, 5 studies were included in the review because they met the inclusion criteria. A flow chart illustrating all selection process is shown in Figure 1. References of the included studies with the relative results are shown in Table 1 and the quality assessment score is shown in Table 2.

Two of the selected studies were cross-sectional [11,12], and three of them were case-control studies [13–15].

Of these, one study carried out by Said *et al*., studied risk factors associated with occult HBV infection, while the other 4 studies assessed risk factors associated with HBsAg positivity.

Said *et al.* [11] conducted a descriptive cross-sectional study in Egypt on 3 167 blood donors negative for HBsAg, hepatitis C virus antibody and HIV antibody. Multivariate logistic analysis revealed that age above thirty years and the marital status were the most significant risk factors for prediction anti-HBc positivity among blood donors [AOR = 1.8; 95% confidence interval (*CI*): 1.4–2.4 and AOR = 1.4; 95% *CI*: 1.0–1.9 respectively].

Among anti-HBc positive blood donors, age above thirty was the most significant risk factor for prediction of HBV-DNA positivity (AOR = 3.8; 95% *CI*: 1.8–7.9).

Other potential risk factors as gender, blood transfusion, diabetes mellitus, frequent injections, tattooing, previous surgery, hospitalization, bilharziasis or positive family history of HBV or HCV infections were not found to be significantly associated with positive anti-HBc antibodies.

A cross-sectional survey among male Saudi voluntary blood donors was conducted by El Beltagy *et al.* [12] in the northwest region of Saudi Arabia. Regarding age, HBV markers were significantly higher in age groups 30–39 years (OR = 5.03; 95% *CI*: 2.64–9.80) and 40 years (OR = 2.99; 95% *CI*: 1.50–6.10) compared to the youngest age group (< 20 years). HBV markers were significantly higher in married subjects compared to unmarried (OR = 1.67; 95% *CI*: 1.39–2.00). Lower educated subjects showed HBV markers significantly higher compared to higher educated (OR = 1.53; 95% *CI*: 1.25–1.9). Both occupations, laborers and military personnel, showed significant association with HBV markers compared to professionals respectively [(OR = 4.0; 95% *CI*: 3.12–5.12) and (OR = 1.97; 95% *CI*: 1.56–2.5)]. The subjects with a family history of HBV infection showed HBV positive markers significantly higher compared to among those without (OR = 3.12; 95% *CI*: 2.6–3.78). No significant association was found regarding history of

Table 1
Results of the included studies.

Author and year of publication	Country	Study design (No. participants)	Risk factor considered		OR or AOR (95% *CI*)
Said *et al*. 2013	Egypt	Cross-sectional (n = 3167)	Age ≥ 30 years		AOR = 1.8 (1.4–2.4)
					AOR = 3.8 (1.8–7.9)
			Married		AOR = 1.4 (1.0–1.9)
Jagannathan *et al*. 2010	India	Case-cohort study (n = 283)	Age 26–45		AOR = 3.60 (1.76–7.39)
			Repeated donor status		AOR = 0.34 (0.17–0.71)
			Residence/rural area	Hosur *vs*. Bangalore	AOR = 0.19 (0.02–1.48)
				Outside *vs*. Bangalore	AOR = 15.66 (3.60–68.07)
			Barber shop		AOR = 4.07 (2.06–8.03)
			Contact with a jaundice/history of jaundice		AOR = 13.64 (3.71–50.24)
			Cigarette smoking		AOR = 3.25 (1.39–7.60)
El Beltagy *et al*. 2008	Saudi Arabia	Cross-sectional (n = 3192)	Age ≥ 30 years	30–39 years	OR = 5.03 (2.64–9.80)
				40 years	OR = 2.99 (1.50–6.10)
			Educational level: Lower education *vs*. higher		OR = 1.53 (1.25–1.90)
			Family history of HBV infection		OR = 3.12 (2.60–3.78)
			Marital status		OR = 1.67 (1.39–2.00)
			Type of occupation	Laborer	OR = 4.0 (3.12–5.12)
				Military	OR = 1.97 (1.56–2.50)
				Professional and student	Not significant results
Akhtar *et al*. 2005	Kuwait	Case-control study (n = 75 752)	Injury resulted in bleeding during shaving from barbers		AOR = 2.3 (1.1–4.8)
			Dental treatment/dental procedure history		AOR = 9.8 (2.1–46.1)
			Type of syringe used for the last injection	Glass syringe by health–care providers	AOR = 9.4 (2.6–34.3)
			History of injections (during the last five years)	1–5 injections	AOR = 3.3 (1.1–9.6)
				> 5 injections	AOR = 1.4 (1.4–12.7)
Nascimento *et al*. 2008	Brazil	Cross-sectional (n = 3598)	Age 25–34 years		OR = 1.73 (1.10–2.80)
			Multiple partners/history of sexual risk behaviors	Men	OR = 1.95 (1.20–3.10)

Table 2
Quality assessment score (Newcastle-Ottawa scale for case-control and adapted for cross-sectional).

Authors (year of publication)	Study design	Selection	Comparability	Outcome	Total score
Said *et al*. [11] (2013)	Cross-sectional	5/5	1/2	3/3	9/10
El Beltagy *et al*. [12] (2008)	Cross-sectional	5/5	2/2	3/3	10/10
Jagannathan *et al*. [13] (2010)	Case-cohort (nested case-control)	4/4	2/2	3/3	9/9
Akhtar *et al*. [14] (2005)	Case-control	4/4	2/2	3/3	9/9
Nascimento *et al*. [15] (2008)	Case-control	4/4	2/2	3/3	9/9

exposure to risky procedures or behaviors. All study subjects previously immunized for HBV in three doses were negative for both HBsAg and anti-HBc.

Jagannathan *et al*. [13] conducted a case-cohort study in Bangalore, India. HBsAg positive cases had significantly higher unadjusted odds of having a body piercing, having a tattoo, shaving at a barber's saloon, having contact with someone with jaundice, smoking, consuming alcohol, having sex with multiple partners, paying for sex, and donating blood to be tested for HIV/AIDS. Behavioral factors associated with HBsAg status, were a repeated donor status (AOR = 0.34; 95% *CI*: 0.17–0.71), and as risk factors residence outside Bangalore (rural area) (AOR = 15.66; 95% *CI*: 3.60–68.07), contact with someone with jaundice (AOR = 13.64; 95% *CI*: 3.71–50.24), being shaved by a barber (AOR = 4.07; 95% *CI*: 2.06–8.03), and cigarette smoking (AOR = 3.25; 95% *CI*: 1.39–7.60).

Akhtar *et al*. [14] conducted an epidemiologic study to better understanding the associated risk factors of chronic infection with HBV in asymptomatic volunteer male blood donors in Pakistan. They showed that cases received more often inadequate and unsafe dental treatment in comparison to the controls (AOR = 9.8; 95% *CI*: 2.1–46.1), as well as received injections (AOR = 3.3; 95% *CI*: 1.1–9.6) or received injection through a glass syringe (AOR = 9.4; 95% *CI*: 2.6–34.3). Another risk factors registered was an injury resulted in bleeding during shaving from barbers (AOR = 2.3; 95% *CI*: 1.1–4.8).

Consecutive first-time, voluntary, unpaid blood donors were recruited by Nascimento *et al*. [15] in Brazil to explore risk

factors associated with HBV infection. The seroprevalence of anti-HBc increased with age among men (*P* trend = 0.0002) and women (*P* trend = 0.0005). The seroprevalence of anti-HBc, but not of HBsAg, was lower among men (OR = 0.51; 95% *CI*: 0.30–0.80) and women (OR = 0.56; 95% *CI*: 0.30–1.00) with a higher education level (secondary or higher). Anti-HBc was associated with lifetime number of sexual partners among men (OR = 1.95; 95% *CI*: 1.20–3.10).

4. Discussion

Occult hepatitis B infection (OBI) is one of the most challenging topics in the field of viral hepatitis [16]. OBI is defined by the presence of HBV DNA in the liver (with detectable or undetectable HBV DNA in the serum) in patients with serological markers of previous infection (anti-HBc and/or anti-HBs positive) or in patients without serological markers (anti-HBc and/or anti-HBs negative). The prevalence of OBI is quite variable depending on the level of endemic disease in different parts of the world, the different assays utilized in the studies, and the different populations studied [17]. Occult HBV may impact in several different clinical contexts, including the transmission of the infection by blood transfusion or organ transplantation and its acute reactivation when an immunosuppressive status occurs [18]. Occult HBV infection in blood donors is considered a potential threat for the safety of the blood supply however conclusive studies on this issue are lacking [19].

Although, the incidence of transfusion-transmitted hepatitis B has been steadily reduced over the last four decades [16], HBV still remains the most frequent transfusion-transmitted viral infection. There is an high variability of infection with HBV across the countries, with high level in prevalence and incidence in developing world such as in Brazil (1.6%–7.7%) [20,21], in Egypt (19.6%) [22], and from various areas of India (2%–10%) [23].

Nascimento *et al*. [15], however, in their Brazilian multicenter sero-survey, reported a low seroprevalences of HBV among first-time voluntary blood donors, a population usually expected to have a higher prevalence of viral hepatitis infection than repeat blood donors [23]. However little data are available on the seroprevalence of, and risk factors for HBV infection in Latin American countries including Brazil [24,25]. In addition, in many developing countries, the relative contributions of various routes of HBV infection have not been defined in population-based studies. Due to a lack of universal and appropriate blood screening in these countries, the risk of post-transfusion HBV infection is still unknown.

The paucity in literature on HBV risk factors among blood donors is especially limited to few areas and most studies targets small groups of individuals. So there is a limited and unclear picture of the HBV risk factors among blood donors worldwide. In addition the few studies carried out have some limitations including the selection bias due to the small sample size where the individuals represent a small proportion of donors.

The study carried out by Said *et al*. [11] proved that OBI exists among Egyptian blood donors. In a study carried out in Egyptian blood donors by Wasfi OA *et al*. [26], the rates were lower than previous studies conducted in Egypt, perhaps due to predonation screening which excludes those known to be at high risk of contacting blood-borne infections or who had other contraindications to blood donation. However, Said *et al*. [11] did not show an association between any of the former risk factors and OBI except for age. Similarly, El Beltagy *et al*. [12] reported that blood donors with positive HBV markers showed significant association with increased age.

The study carried out by Nascimento *et al*. [15] reported that the seroprevalence of anti-HBc increased with age among men and women. Allain *et al*. [27] found that OBI donors are generally older than 45 years except in Africa while Minuk *et al*. [28], demonstrated that age, gender do not identify those with OBI.

In addition, El Beltagy *et al*. [12] showed significant association with married status, specific occupations such as blue collar worker and the military, family history of HBV infection, lack of immunization, lower educational level. In general population low educational attainment had been associated with higher prevalence of hepatitis B in both developed and developing countries. In the study carried out by Nascimento *et al*. [15], there was a lower risk of past exposure to HBV among male and female blood donors who reported a higher education level.

Moreover, in low socio-economic settings, horizontal transmissions of HBV through contact with infected family member have also been reported [29]. El Beltagy *et al*. [12] did not find a significant association with history of exposure to high-risk procedure or behavior while in literature parenteral routes are implicated as the most likely factors for HBV transmission that include unsterilized needles and syringes in health-care settings [30,31]. In their study, Akhtar *et al*. found that dental care provider and injections are risk factors [14]. In the general population, history of repeated blood transfusions [32], history of injections [33], including re-use of contaminated syringes, contaminated surgical instruments and blood products [34]; number of pregnancies [35]; hemodialysis [36]; tooth extraction [32]; dental procedures, needle prick and surgical procedures for health care workers [37]; unsafe surgery [38] are the main risk factors. On the other hand, a recent study conducted in Egypt showed that HBV transmission is community rather than iatrogenic-acquired [39]. Behavioral risks as intravenous drug use, needle stick injuries, tattooing and multiple sexual partners have been identified as common modes of HBV transmission in the developed world [39]. Nascimento *et al*. [15] however found that anti-HBc was associated with lifetime number of sexual partners among men, but not among women and there was no relationship between sexual behavior and the seroprevalence of HBsAg in either gender. Jagannathan *et al*. [13] found several demographic and behavioral risk factors are associated with HBsAg status among blood donors in Bangalore, India: first-time donor status, contact with a jaundiced person, associations with place of residence and patronage of local barbers that may have relevance for blood safety and public health. This risk factor is confirmed by Akhtar *et al*. [14] where injury resulted in bleeding during shaving from barbers was also significant predictor of HBsAg positivity. In general population, history of jaundice [14], rural origin and shaved by barber are also the main risk factor reported. However, Jagannathan *et al*. emphasized the need for further epidemiologic research because of sample size [13].

It's important to emphasize the importance of hospital risk prevention as well as health education among population and better training in the domain of blood safety and in healthcare workers [33–40].

Baha *et al*. showed that in Marocco there is a lower prevalence of HBV and HCV in blood donors in comparison to the

general citizens, emphasizing that the blood transfusion was not a predictor for transmission but the main risk originated from the hospital exposure to contaminated instruments [41].

Infection control measures in health-care settings include safe injection practices and proper sterilization techniques of medical instruments as well as barber's instruments, and the reuse of razors in the barber shops need to be discouraged, emphasizing the sterilization.

Preventive strategies for HBV infection include healthy blood transfusion services and vaccination against HBV [42].

The agenda of every national blood programme should be focused on the implementation of effective quality systems, as well as the development and implementation of quality standards, effective documentation systems, training of all staff and regular quality assessment to ensure that all donated blood is screened for transfusion-transmissible infections [43].

Globally, however, there are significant variations in the extent to which donated blood is screened, the screening strategies adopted and the overall quality and effectiveness of the blood screening process. As a result, in many countries the recipients of blood and blood products remain at unacceptable risk of acquiring life-threatening infections that could easily be prevented.

There is a need of a public awareness programs especially in rural areas and people at high risk to decrease the burden of HBV infection. Each country should establish voluntary blood donor programmes which provide donor information and education [1].

Prevention might be achieved through a more rigorous screening for history of risk behaviors and risk factors during the donor selection process to collect blood from well-selected, voluntary non-remunerated blood donors from low-risk populations, particularly those who donate regularly [44]. Paid blood donation should be prohibited [45].

5. Conclusions

HBV remains the infection most frequently recognized by donation testing in blood donors. It's a cause of significant morbidity and mortality in certain ethnic populations and among groups of people whose behavior puts them at high risk.

Our research shows that there is a nonuniform pattern of distribution throughout the countries/regions, with HBV prevalence related to geographical, social and cultural factors that predispose certain individuals to infection. The mode of HBV transmission differs throughout the countries (Table 1). Transmission occurs by the same routes as in various parts of the world: through percutaneous or permucosal exposure to infected blood or other secretions. In Brazil, the predominant means of transmission are sexual intercourse. Barber shop transmission plays an important role in areas as in Kuwait and in India. In Kuwait, there are inadequate measures to block transmission through injections or dental treatment/dental procedure. The repeated donor status is a source of disease transmission that must be considered in India.

However, other socio-demographic, environmental, socio-cultural factors specific to the geographical site may contribute to the unique characteristics of the infection observed in these countries (as the marital status in Egypt, living in residence/rural area in India, the occupation and the educational level and the family history of HBV infection in Saudi Arabia).

Because HBV infection mostly reflects the country of origin of the donor and it's different by different geographical region, the obtained data encourage to conduct further research among blood donors throughout other regions in order to fully understand risk factors among donors in more extensive areas and at national level worldwide, thus to provide valuable information about surveillance, therefore to adopt targeted policies concerning the adoption of precautionary measures in order to reduce the residual specific risk of HBV and to introduce appropriate changes in donor selection guidelines.

Conflict of interest statement

We declare that we have no conflict of interest.

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