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Women and Girls with Hemophilia Receiving Care at Specialized Hemophilia Treatment Centers in the United States

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Summary

Introduction: Females may have hemophilia with the same factor VIII (FVIII) or factor IX (FIX) levels as affected males. Characterization of females with hemophilia would be useful for health care planning to meet their unique needs. Federally-funded Hemophilia Treatment Centers (HTCs) in the United States contribute data on all individuals with bleeding disorders receiving care to the Population Profile (HTC PP) component of the Community Counts Public Health Surveillance of Bleeding Disorders project.

Aims: To estimate the number of females with hemophilia receiving care at HTCs in the U.S. and compare their characteristics with those of males with hemophilia.

Methods: HTC PP data collected on people receiving care at an HTC from January 2012 through September 2020 with hemophilia A and B were evaluated by sex for demographic and clinical characteristics.

Results: A factor level <40% was reported for 23,196 males (97.8%) and 1,667 females (47.6%) attending HTCs; 51 (0.48%) severe, 79 (1.4%) moderate, and 1,537 (17.9%) mild hemophilia patients were female. Females were older, more often White, and less often non-Hispanic than males. Females were less likely to have history of HIV or HCV infection, even among those with

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DISCLOSURES

CHM, JMS, and ABP designed the study, conducted the research, analyzed the data and wrote the paper. VRB, RFS, TWB, and CJB conducted the research and wrote the paper. RLS has participated as a paid consultant to Bayer, Biomarin, uniQure, Spark, Novo Nordisk, Genentech/Roche, Octapharma, Takeda, Catalyst, Guardian Therapeutics, Pfizer, Hema Biologics, and Sanofi/Sobi and has investigator initiated grants from Octapharma, Genetech, Grifols, and Takeda. TWB has acted as a paid consultant to BioMarin, Tremeau Pharmaceuticals, and uniQure and has participated in advisory boards with Takeda, Pfizer, CSL Behring, Genentech/Roche, Spark, Novo Nordisk, Spark, and Bayer. All other authors stated that they had no interests which might be perceived as posing a conflict or bias.

severe disease, but twice as likely to have infection status unknown. Females with mild hemophilia were more often uninsured than males.

Conclusions: Females with severe or moderate hemophilia are uncommon, even in specialized care centers; however, almost 1 in 5 patients with mild hemophilia was female, indicating needs for specialized care based on factor level and history for affected females.

Keywords

Factor VIII; factor IX; hemophilia A; hemophilia B

INTRODUCTION

Historically, hemophilia was considered to affect males and be transmitted through unaffected females with limited recognition of its occurrence in women and girls. Today, it is known that women and girls can have hemophilia A (HA) or hemophilia B (HB) for a variety of genetic reasons [1]. Females require the same doses and frequencies of factor infusions as affected males with similar factor VIII activity (FVIII) or factor IX activity (FIX) levels and, similar to males, require an individualized approach depending on bleeding phenotype. The actual number of females requiring care is unknown. Estimates would be useful for health care planning and resource management to meet the unique needs of females with hemophilia.

Approximately 250 cases of “female hemophilia” have been reported in the literature worldwide [1]. Case reports, however, do not accurately reflect the number of affected females. More useful data can come from surveillance programs. Two limited studies of women and girls with hemophilia have been conducted using data from the United States Hemophilia Treatment Centers Network (USHTCN). Byams et al [2] in 2011 reported 40 females with HA and 11 with HB with factor levels <50% from 20 federally-funded hemophilia treatment centers (HTCs) in the United States piloting a female-specific surveillance form. In 2014, DiMichele et al [3] found that 75% of 32 responding U.S. HTCs reported treating at least one female with severe or moderate hemophilia and described 17 females with HA and 5 females with HB with factor levels ≤5%. These reports represented only a minority of the more than 135 federally funded HTCs in the United States at that time; further, the reports were necessarily limited to those who elected to participate in the comprehensive data collection programs (i.e., registries) at those HTCs. The Community Counts Public Health Bleeding Disorders Surveillance project, a collaborative project of the USHTCN, the American Thrombosis and Hemostasis Network (ATHN), and the Centers for Disease Control and Prevention (CDC) was initiated in 2012 [4]. Community Counts expanded on a previous surveillance program among federally-funded HTCs in several ways. In addition to collecting detailed data from persons with bleeding disorders who agree to be included in a registry, Community Counts also includes a new component, known as the HTC Population Profile (HTC PP), in which limited data on all persons receiving care at HTCs are collected; these de-identified data submissions do not require participant enrollment. The aims of this study were to use data from the HTC PP to estimate the number of women and girls with hemophilia A or B receiving care at HTCs in the United States

and to compare their characteristics with those of men and boys with hemophilia attending HTCs.

MATERIALS AND METHODS

In January 2012, HTC staff began collecting Community Counts HTC PP data on all people with bleeding disorders who visited an HTC for diagnosis or care; data were collected using standardized forms [4, 5]. Valid qualifying visit types for inclusion in the HTC PP are comprehensive, consultation, non-office, office, or study (research participation) visit. Demographic and clinical data are de-identified prior to transmission to CDC using a unique identification code known only to HTC staff. Participant authorization for inclusion in the HTC PP was not required at most HTCs because HTC PP data are de-identified and this project was designated as public health surveillance by CDC. One of the 139 HTCs required participant authorization for inclusion. Data elements pertinent to this study include year of birth, sex, race, Hispanic ethnicity, 3-digit zip code of residence, health insurance status, primary bleeding disorder diagnosis, baseline factor activity level, history of hepatitis C (HCV) infection, and history of human immunodeficiency virus (HIV) infection. Insurance coverage included one or more of the following U.S. health insurance types: Medicare, Medicaid, commercial insurance, state high risk insurance pools, Indian Health Service, or TRICARE (military).

Data collected on unique individuals with a primary diagnosis of HA, specified as “Hemophilia A (factor VIII deficient) including carriers,” or HB, specified as “Hemophilia B (factor IX deficient) including carriers,” who received care in 139 federally supported HTCs in the U.S. (Guam and Puerto Rico territories were excluded) during the period 2012 through September 2020 were included in this analysis. HA or HB was classified as severe if the baseline factor activity level was <1%, moderate if 1-5% and mild if >5% and <40% of normal using criteria established by the International Society on Thrombosis and Haemostasis (ISTH) [6]. The distributions of the patients according to clinical (hemophilia type and severity) and demographic (age, sex, race and ethnicity) characteristics were used to describe the populations receiving care. Fifteen subjects reporting sex other than male or female were excluded. The number of visits during the study period was counted for each patient and the percent of possible visits was calculated as the number of visits divided by the total annual visits possible from each patient’s initial visit date until the end of the surveillance period.

Data were analyzed using SAS Version 9.4 (SAS Institute, Cary, NC, USA). Groups were compared using Chi-square and Fisher’s exact tests, as appropriate, with significance level set at $P<0.05$.

RESULTS

During the period 2012 through September 2020, 27,232 individuals classified under the diagnosis of HA or HB attended the 139 federally supported HTCs in the U.S. at least once, including 23,728 males and 3,504 females (Table 1). Factor levels were reported as unknown for 226 males (1.0%) and 273 females (7.8%). The distributions of FVIII and

FIX levels in all female subjects with reported levels are shown in Figure 1. Mean FVIII level of 2,269 female subjects was 44.1%; mean FIX level of 962 female subjects was 40.7%. A total of 23,196 males (97.8%) and 1,667 females (47.6%) met the diagnostic criteria for severe, moderate, or mild hemophilia.[6] A higher proportion of females (1,564; 44.6%) than males (306; 1.3%) had factor levels ≥40% and may have attended the HTCs for reasons such as consultation for bleeding symptoms or genetic testing but not have met the diagnostic criteria used here. The number of visits during the study period by sex and hemophilia severity are shown in Figure 2. Females had significantly fewer visits than males in all severity categories. The wider 95% confidence limits (CL) for females reflect the smaller numbers of females than males in each group. Females with factor levels in the mild category had significantly more visits than those with factor levels greater than 40% (mean 2.13; 95% CL 2.04-2.21 vs. 2.88; 95% CL 2.77-2.99). Visits calculated as percent of possible visits during the study period gave similar results (data not shown). Individuals with factor level reported as greater than 40% were excluded from further analysis as not meeting the ISTH diagnostic criteria used for hemophilia.

The diagnoses reported for the study group are shown in Table 2 by sex, hemophilia type, and severity. As would be expected, the distributions of severity for males and females were significantly different ($P<0.0001$). Severe disease in females was quite rare, occurring in only 51 cases and making up less than 0.5% of those with severe HA or HB. Females with moderate hemophilia were slightly more common, and the 79 individuals in this category comprised 1.8% of subjects with HA and 0.9% of those with HB. In contrast, 16.1% of subjects with mild HA and 23.7% of subjects with mild HB were female. Among subjects with mild HA, males had a mean FVIII level of 15% vs. 27% among females. For mild HB, males had a mean FIX level of 13% vs. 26% among females.

The demographic characteristics of the study population by sex and hemophilia type are shown in Table 3. Among males, 76.4% had HA and 23.6% had HB, while 69.4% of females had HA and 30.6% had HB ($P<0.0001$). The age distributions of males and females were significantly different ($P<0.0001$). Females were older with mean age 31.4 years vs. 27.9 years for males; 64.5% of females were age 20 years or greater compared to 58.1% of males. The race distributions were also significantly different by sex ($P<0.0001$), with White race more common and Black/African-American and Asian less common among females compared to males. Non-Hispanic ethnicity was less common among females ($P<0.0001$). For both race and ethnicity, however, the unknown categories were greater for females than for males, perhaps influencing these figures.

Positive history of HIV was less common in females with hemophilia than males, 0.6% vs. 6.1% overall ($P<0.0001$) (Table 4A). Among those with severe hemophilia, 1,057 males (10.0%) and only 2 females (3.9%) had a positive history ($P=0.036$). For HCV infection (Table 4B), 21.0% of males and 3.6% of females were reported to have a positive history ($P<0.0001$); among those with severe hemophilia, 26.2% of males and 11.8% of females reported HCV infection ($P=0.004$). For both infections, females were twice as likely to have their status reported as unknown. Overall, 91.0% of females and 93.4% of males were insured ($P<0.0001$), although the differences were not significant for the severe and moderate groups (Table 5).

DISCUSSION

Almost 1 in 5 patients seen for mild hemophilia during the study period was female; while females with severe or moderate hemophilia were uncommon, even in specialized care centers, with only 130 being identified in this study throughout the U.S. In addition to experiencing the same bleeding symptoms as males, females have the additional risk factors of menstruation, childbearing, and menopause that may require treatment. They join women with von Willebrand disease and rare factor deficiencies in the need for specialized care to improve quality of life and minimize complications [2, 7].

Females may exhibit the hemophilia phenotype for a variety of reasons [1]. Those who are homozygous, compound heterozygous, or hemizygous for hemophilia alleles are genetically identical to males with hemophilia and will have FVIII or FIX activity levels equivalent to those of affected males in the same families. In addition, heterozygous females may exhibit the hemophilia phenotype because they have preferential X-chromosome inactivation (XCI), causing the X bearing the normal allele to be inactive in all or most cells; however, these occurrences are rare. As a group, heterozygotes, who are often called carriers, have factor VIII or IX activity levels that are widely distributed with a mean near 50%, overlapping both the normal range and the range considered diagnostic of hemophilia; therefore, half of heterozygotes will have factor levels below 50%. The distributions of FVIII and FIX levels seen among women and girls attending HTCs were similar to those expected for heterozygotes for hemophilia. Their mean factor levels of 44% FVIII and 41% FIX are slightly lower than those reported for genetically proven heterozygotes [8, 9]. It has been estimated from distributions of heterozygotes not selected for bleeding symptoms that about 28% would have factor levels below the hemostatic level of 40% [8, 10]. However, among the females seen in the USHTCN, 52% had factor levels less than 40%. Enrichment for women and girls with symptoms, and thus lower levels, would be expected in the population attending HTCs. Females with factor levels >40% may include asymptomatic family members seen only for genetic testing, which would ordinarily require two visits. Those with FVIII or FIX above 40% had significantly fewer HTC visits, averaging two, than those with lower levels, averaging three. For purposes of this analysis, we excluded women and girls not meeting the ISTH definition for hemophilia. Some females with factor levels greater than 40% may experience bleeding [8, 9], perhaps due to the discrepancies in FVIII levels measured with one-stage clotting assays versus chromogenic assays associated with some variants [9] or to the presence of a structurally abnormal molecule with poor function *in vivo* from non-null variants [11]. This is an area requiring further study. Because the HTC PP does not collect data on hemophilia treatment, analysis of actual treatment experience in the female population in this study was not possible. It would be worthwhile to examine the bleeding manifestations and treatment of females with various factor levels in the smaller registry component of Community Counts, which has such data available [4].

Hemophilia heterozygotes have increased rates of excessive bleeding with surgery, tooth extraction, and delivery, as recently reviewed [1, 12]. FVIII and FIX levels in heterozygotes have been reported to correlate inversely with bleeding scores in some studies [9, 13]; however, these correlations were relatively weak. Because FVIII levels rise with age in heterozygotes [14], an adult woman’s current FVIII level may not reflect her lifelong

history. In contrast, FIX levels are low in infancy but do not appear to change with age after that period among heterozygotes [15]. Bleeding scores and other retrospective analyses may include excessive bleeding occurring at a point in a woman's life in which she had a lower factor level. However, a U.S. study found hemarthrosis within the previous 6 months in 54% of females with severe, 36% with moderate, 15% with mild HA, and none with normal levels [16]. Although the group of females with mild hemophilia had factor levels higher than their male counterparts in this study and thus may experience fewer hemarthroses [17], these levels may not be sufficient to protect them from the challenges of menstruation and childbirth that males do not experience. Definitions of hemophilia severity [6] are based on experience with male patients. Evaluation of FVIII and FIX levels required for hemostasis, particularly in the settings of menstruation and childbirth, would be useful.

Females with hemophilia appeared to be slightly but significantly more likely than males to have HB rather than HA. This could result from some females with HA being misdiagnosed as having VWD, which exhibits FVIII deficiency affecting both males and females. However, a higher rate of symptomatic females in HB than in HA was postulated by Graham in 1975 [18]. He reasoned that at the early stage of development at which XCI occurs, more cells leading to production of FVIII would be present, since it is produced in multiple organs by way of endothelial cells [19, 20], than those leading to FIX, which is produced solely in the liver [21]. Fewer precursor cells would mean that a larger proportion of daughter cells would have extreme skewing of XCI and thus more heterozygotes with symptoms would occur in HB. No studies to date have had sufficient numbers of heterozygotes to allow testing of that hypothesis, although the data presented here support the concept.

Females were significantly less likely than males to have a history of HIV or HCV infection, even in the severe category. These variables are likely to be age-related, since infections were more common when untreated blood products were used in the past; however, the females were older than the males (Table 3). A more likely cause may be decreased testing among females, who were twice as likely as males to have their status for these infections unknown. A lower rate could be indicative of either a lower rate of exposure to blood products, perhaps indicating less treatment, or the failure to apply the same monitoring protocols to females that are used for males. Females in the mild hemophilia category were less likely than males to have health insurance coverage, perhaps limiting their access to testing and treatment, although there was no difference in health insurance status by sex in those with severe and moderate disease.

Whites were overrepresented and Blacks and Asians under-represented among both males and females with hemophilia, compared to their numbers in the general population, perhaps reflecting inadequate access to care among US minority populations. Hispanic ethnicity, however, did not differ from expectation. Female patients with hemophilia were less likely than males to have complete demographic information collected, limiting evaluation of differences that might reflect differential access to care, and were less likely to have had important viral testing performed. Among all patients visiting the HTCs, females were much less likely to have had their factor levels measured, which is recommended for all of those undergoing genetic testing [22], as well as being required for treatment decisions. These discrepancies would need to be addressed by care providers to ensure equity.

Classification of females for treatment purposes should be based on their factor activity levels and history, rather than the genetic basis for their disease [1]. Designation of women and girls with low factor activity levels as having hemophilia like their male counterparts rather than as carriers, which has been the practice historically, would help them to receive appropriate treatment and reimbursement for care and, perhaps, decrease their reported negative experiences with the health care system [23]. Further research is required to determine whether current factor level is sufficient to assess bleeding risk. Continued inclusion of women and girls in registries and ensuring complete data collection is critical to understanding of this population, as well as assuring equitable access to care and allocation of resources.

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DATA AVAILABILITY STATEMENT

The Community Counts surveillance data are available via a data visualization tool that displays de-identified data on patients with bleeding disorders who are enrolled in Community Counts in an interactive, visual format (https://www.cdc.gov/ncbddd/hemophilia/communitycounts/data-viz.html). However, due to ethical restrictions related to protecting patient confidentiality, additional individual-level data generated from the Community Counts surveillance system cannot be made publicly available.

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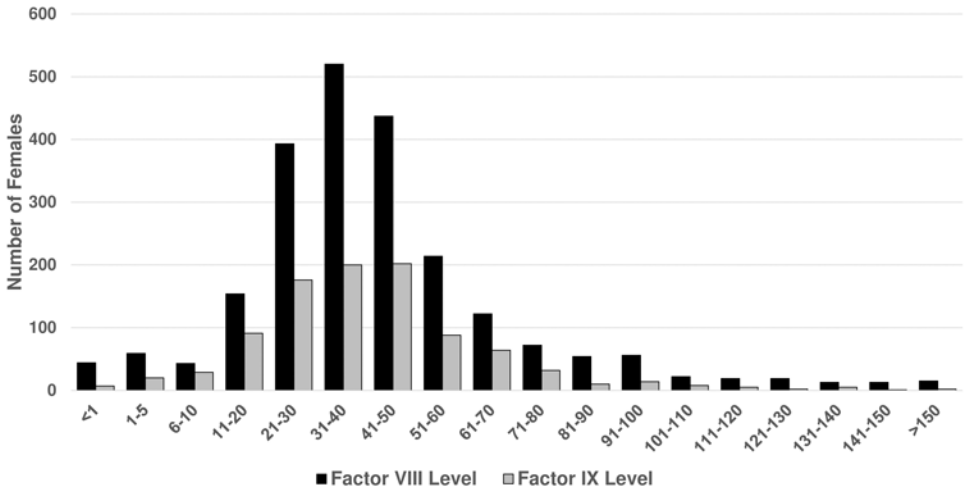

Figure 1.
Distribution of factor levels for females attending U.S. hemophilia treatment centers

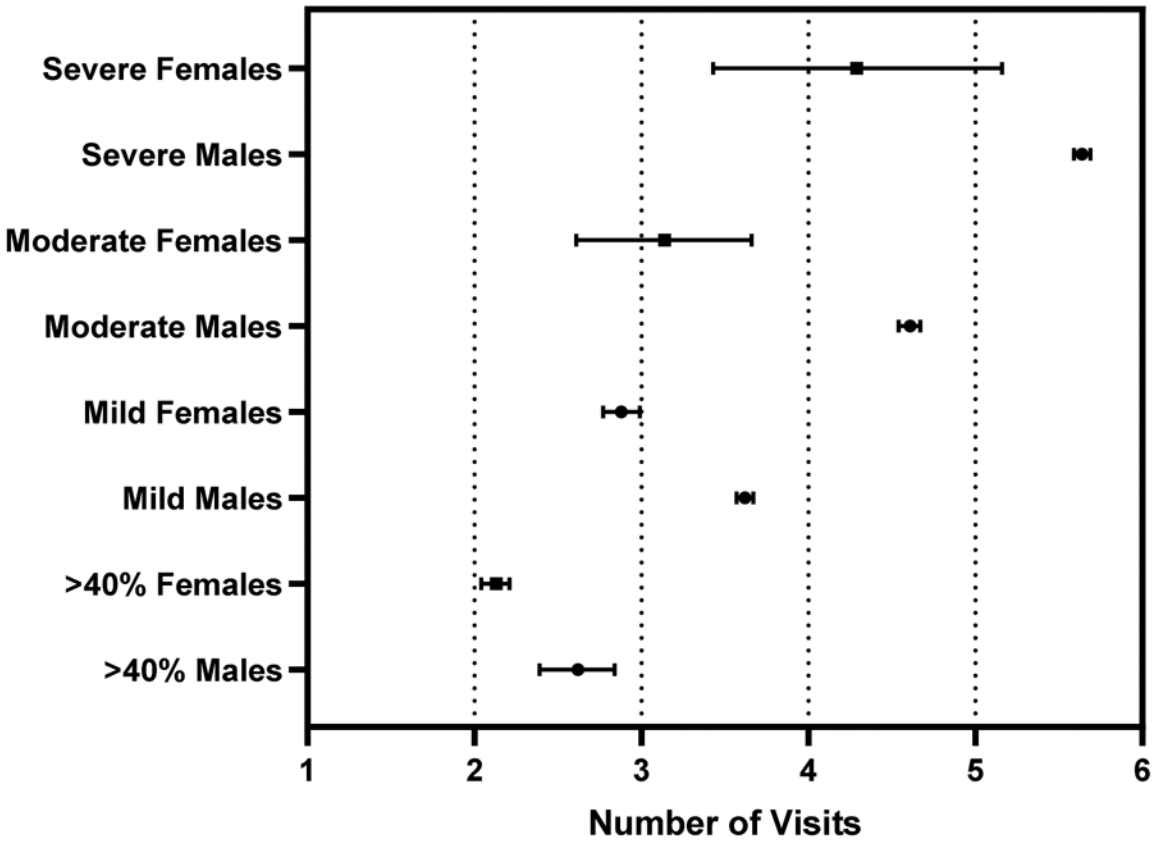

Figure 2.
Mean and 95% confidence limits for number of visits during the study period (2012-2020) by sex and severity

Table 1.

Individuals attending hemophilia treatment centers in the United States from 2012 through September 2020 under the diagnostic category of hemophilia, including carriers

Characteristics	Males		Females	
	n	%	n	%
Hemophilia A				
Severe <1%	8,916	49.3	44	1.8
Moderate 1-5%	3,294	18.2	59	2.4
Mild >5 and <40%	5,506	30.4	1,054	42.2
>40%	225	1.2	1,112	44.6
Unknown	161	0.9	226	9.0
Total	18,102		2,495	
Hemophilia B				
Severe <1%	1,638	29.1	7	0.7
Moderate 1-5%	2,286	40.6	20	2.0
Mild >5 and <40%	1,556	27.7	483	47.9
>40%	81	1.4	452	44.8
Unknown	65	1.2	47	4.6
Total	5,626		1,009	
Hemophilia A and B				
Severe <1%	10,554	44.5	51	1.4
Moderate 1-5%	5,580	23.5	79	2.3
Mild >5 and <40%	7,062	29.8	1,537	43.9
>40%	306	1.3	1,564	44.6
Unknown	226	0.9	273	7.8
Total	23,728		3,504	

Table 2.

Individuals with factor levels diagnostic of hemophilia attending hemophilia treatment centers in the United States from 2012 through September 2020

	Severe				Moderate				Mild				All Severities			
	Males		Females		Males		Females		Males		Females		Males		Females	
	n	%	n	%	n	%	n	%	N	%	n	%	n	%	n	%
Hemophilia A *	8,916	99.5	44	0.49	3,294	98.2	59	1.8	5,506	83.9	1,054	16.1	17,716	93.9	1,157	6.1
Hemophilia B *	1,638	99.6	7	0.43	2,286	99.1	20	0.9	1,556	76.3	483	23.7	5,480	91.5	510	8.5
Hemophilia A & B *	10,554	99.5	51	0.48	5,580	98.6	79	1.4	7,062	82.1	1,537	17.9	23,196	93.3	1,667	6.7

* Severity distribution between males and females significantly different (P<0.0001)

Table 3.

Demographic characteristics of the study population

Characteristics	Males		Females	
	n	%	n	%
Hemophilia Type *				
Hemophilia A	17716	76.4	1157	69.4
Hemophilia B	5480	23.6	510	30.6
Age (years) *				
Under 1	203	0.9	11	0.7
1 – 5	2096	9.0	108	6.5
6-11	2941	12.7	159	9.5
12-19	4475	19.3	313	18.8
20-29	4497	19.4	272	16.3
30-39	3226	13.9	273	16.4
40-49	1870	8.1	191	11.5
50-59	1682	7.3	148	8.9
60-69	1290	5.6	118	7.1
70+	916	3.9	74	4.4
Race *				
White	18636	80.3	1416	84.9
Black	2600	11.2	98	5.9
Asian	867	3.7	42	2.5
Other	511	2.2	34	2.0
Unknown	582	2.5	77	4.6
Ethnicity *				
Non-Hispanic	19115	82.4	1349	80.9
Hispanic	3814	16.4	276	16.6
Unknown	267	1.2	42	2.5

* Distributions are significantly different between males and females (P<0.0001).

Table 4.

History of blood-borne infections reported in the study group

Characteristics		Males		Females		*P*-value
		n	%	n	%	
A. Human Immunodeficiency Virus (HIV)						
Severe	Yes	1057	10.0	2	3.9	0.036
	No	8850	83.9	42	82.4	
	Unknown	647	6.1	7	13.7	
Moderate	Yes	224	4.0	3	3.8	NS
	No	4804	86.1	68	86.1	
	Unknown	552	9.9	8	10.1	
Mild	Yes	127	1.8	5	0.3	<0.0001
	No	6095	86.3	1248	81.2	
	Unknown	840	11.9	284	18.5	
All	Yes	1408	6.1	10	0.6	<0.0001
	No	19749	85.1	1358	81.5	
	Unknown	2039	8.8	299	17.9	
B. Hepatitis C Virus (HCV)						
Severe	Yes	2762	26.2	6	11.8	0.004
	No	7233	68.5	38	74.5	
	Unknown	559	5.3	7	13.7	
Moderate	Yes	1091	19.6	8	10.1	NS
	No	3999	71.7	64	81.0	
	Unknown	490	8.8	7	8.9	
Mild	Yes	1021	14.5	46	3.0	<0.0001
	No	5281	74.8	1211	78.8	
	Unknown	760	10.8	280	18.2	
All	Yes	4874	21.0	60	3.6	<0.0001
	No	16513	71.2	1313	78.8	
	Unknown	1809	7.8	294	17.6	

Table 5.

Health insurance status reported in the study group

Characteristics		Males		Females		*P*-value
		n	%	n	%	
Severe	Insured	10,101	95.7	48	94.1	NS
	Uninsured	259	2.5	2	3.9	
	Unknown	194	1.8	1	2.0	
Moderate	Insured	4907	87.9	68	86.1	NS
	Uninsured	583	10.4	11	13.9	
	Unknown	90	1.6	0	0	
Mild	Insured	6657	94.3	1401	91.1	<0.0001
	Uninsured	295	4.2	110	7.2	
	Unknown	110	1.5	26	1.7	
All	Insured	21665	93.4	1517	91.0	<0.0001
	Uninsured	1137	4.9	123	7.4	
	Unknown	394	1.6	27	1.6	