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Seroprevalence and Seroincidence of Herpes Simplex Virus (2006–2010), Syphilis (2006–2010) and Vaccine-Preventable Human Papilloma Virus Subtypes (2000–2010) Among United States Military Personnel

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Abstract

Background—Sexually transmitted infections (STI) have historically been burdensome in military populations. We describe the seroprevalence and seroincidence of vaccine-preventable human papillomavirus (VP-HPV) subtypes in a sample of 200 servicemen along with the seroprevalence and seroincidence of herpes simplex virus (HSV-1/2) and syphilis in a sample of 200 males and 200 females.

Methods—Sera from 200 males along with associated demographic data were obtained and tested for HPV serotypes at service entry and ten years later. Similarly, 200 active-duty males and 200 active-duty females were tested for HSV-1/2 at entry to service and four years later.

Results—The baseline prevalence of VP-HPV subtypes was 14.5%, and cumulative seroincidence of new infection was 34% over a 10-year period (n=68). Of these, 63% (n=43) represented HPV-6, HPV-11 or both; 18% of new infections were either HPV-16 or HPV-18, and 19% (n=13) were a mixture of all four strains. At entry to military service, 33.5% of males were seropositive for HSV-1 and 1.5% positive for HSV-2; seroincidence was 3.4 and 1.1 per 100 person-years, respectively. Among females, 39% were seropositive for HSV-1 and 4.0% for HSV-2; seroincidence was 5.5 and 3.3. per 100 person-years, respectively. There were two prevalent and three incident cases of syphilis.

Conclusions—STIs in military populations are highly prevalent, incident, and epidemiologically distinct. Our data show rates of HPV and HSV-1/2 acquisition that are higher

Conflicts of Interest: None.

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than those seen in the general public, again highlighting the need for continued preventive efforts. Consideration of universal HPV vaccination among males is warranted.

Keywords

human papilloma virus (HPV); herpes simplex virus (HSV); military; HPV vaccine

Introduction

The burden of sexually transmitted infections (STIs) among military personnel is significant, and STI-related syndromes have been among the most common of illnesses affecting servicemen and servicewomen throughout history.¹ The incidence and prevalence of STIs within the military, particularly gonorrhea and chlamydia, are frequently reported to be higher than in age-matched civilian populations.^{2–5} Much less is known, however, with respect to viral STIs including herpes simplex virus (HSV-1/2) and human papillomavirus (HPV), particularly among military men. Similarly, studies of the incidence of HSV and vaccine-preventable HPV (VP-HPV) subtypes in the general population are also lacking.

With the availability of a vaccine, and new HPV serotype specific diagnostic tests, opportunities are now present to examine the epidemiology of HPV infection among understudied groups. We recently reported a 14.5% seroprevalence of HPV infections caused by VP-HPV subtypes 6, 11, 16 and 18 among a random sample of men entering military service,⁶ which is two to three times higher than National Health and Nutrition Examination Survey (NHANES) estimates for men aged 20 to 29 years.⁷ Cumulative seroincidence of VP-HPV was 34.2% after 10 years of service, with more than one-third of incident infections involving oncogenic serotypes 16 and 18.

Here, we provide additional serotype-specific details of VP-HPV seroprevalence and seroincidence after ten years of military service. We also report on the seroprevalence and four-year seroincidence of HSV-1/2, as well as syphilis, among 400 randomly selected men and women joining active-duty service.

Materials and Methods

We obtained sera and demographic data from a random sample of active-duty Army and Navy/Marine Corps personnel who entered service in the year 2000 (HPV) and 2006 (HSV, syphilis) using samples archived in the Department of Defense Serum Repository and records from the Defense Medical Surveillance System.⁸ Demographic data included age, race, marital status, education level, rank and Armed Forces Qualifying Test (AFQT) score, which is used to determine service eligibility. Qualifying individuals were stratified into eight U.S. census regions based on their home state of record, with 25 individuals per region comprising a total of 200 men and women, respectively.

HPV testing was restricted to males because of abundant data on HPV infection among women in the military.^{9–11} The sera of 200 active-duty males between 17 and 26 years of age were sampled within one year of entry to service (accession) and then again at their tenth year of service (+/- 1 year), an interval chosen to ensure an adequate number of

incident infections. We tested samples using a commercially available, validated assay (Luminex, PPD Vaccines and Biologics, Wayne, PA) to examine the presence of antibodies to HPV subtypes 6, 11, 16, and 18.^{12,13} Individuals were classified as positive or negative according to published assay cutoffs.¹³

To examine seroprevalence and seroincidence of HSV-1, HSV-2 and syphilis, we obtained sera of 200 men and 200 women randomly sampled in the same fashion described above. We utilized a shorter time interval (four years) to ensure an adequate number of incident infections and to simulate a typical length of an initial military duty tour. This early period of service is also of specific interest for STI prevention efforts given the ease with which each infection can perpetuate over time when not identified early. To identify HSV-1/2 seroconversions, we utilized an IgG enzyme immunoassay (EIA) antibody test (Bioplex Immunoassay, Bio-Rad Laboratories, Hercules, CA) to simultaneously test for HSV-1 and HSV-2 IgG antibodies. While less commonly used in surveillance studies, this assay has demonstrated sensitivity and specificity greater than 97% for HSV-1 and HSV-2 and 97% agreement between this assay and the more commonly used HerpeSelect (Focus Diagnostics, Cypress, CA).^{14,15} Last, we used a treponemal IgG antibody test (Wampole ELISA II, Inverness Medical Laboratories, Princeton, NJ) to identify incident and prevalent cases of syphilis.

Prevalent HPV cases were defined by seropositivity for one or more VP-HPV serotypes at accession. Infection with any new VP-HPV subtype ten years later (± 1 year) was considered an incident case. Thus, incident infection could be observed among those with a baseline infection at accession due to seroconversion to different serotypes. We also examined the proportion of new seroconversions among individuals who were previously seronegative to all VP-HPV subtypes. The one-way ANOVA test was used to compare mean values and the chi-squared test was used to compare proportions and test independence. A significant finding was defined throughout the study as an alpha measure of <0.05 and two-sided p-values were always used. Univariate and multivariate analyses were completed using logistic regression. Odds ratios (OR) are presented with 95% confidence intervals (CI) and p-values. Analysis was performed using SAS software, version 9.3 (Cary, NC).

Results

Baseline prevalence of any VP-HPV subtype among men was 14.5% (Table 1), and the subjects' mean age at accession was 20 years old (st dev ± 2.29). In multivariate analysis adjusted for military rank, single marital status remained an independent predictor of prevalent infection (OR = 4.1, [95% CI 1.3, 13.3]). Due to assay failure for one subject, we were able to analyze incident HPV data for 199 subjects. The cumulative seroincidence with any VP-HPV subtype was 34% (n=68); of these, 63% (n=43) were exclusively HPV-6 or HPV-11, 18% (n=12) were exclusively HPV-16 or HPV-18), and 19% (n=13) were mixed. Among the 68 incident cases, 49 (72%) showed evidence of new infection with only one serotype, 17 (25%) with two serotypes, and 2 (3%) with three types (Table 2). The most common incident serotype of HPV was type 6, which was present in 79% (54/68) of all

incident cases. No demographic factors were significantly associated with seroincidence for any of the VP-HPV subtypes.

In the sample of 200 men and 200 women for HSV and syphilis, women were significantly more likely than men to be African-American, have some college education, and be in the Navy as opposed to Marines ($p<0.05$ for all comparisons). Baseline demographics are presented in Table 3, with seroincidence data in Table 4. Overall, 39% of females were seropositive for HSV-1, 4.0% were positive for HSV-2, and 1.5% were positive for both at service entry, with incidence rates of 5.5 per 100 person-years for HSV-1 and 3.3 for HSV-2. Among males at service entry, 33.5% were seropositive for HSV-1, 1.5% were positive for HSV-2, and 1.5% were positive for both; seroincidence was 3.4 per 100 person-years for HSV-1 and 1.1 for HSV-2.

Among prevalent cases (Table 3), men with HSV-1 were significantly ($p<0.05$) more likely to have lower AFQT scores than men without HSV-1, and HSV-2 was significantly more prevalent among female Marines than those in other service branches ($p<0.05$). In turn, a significantly higher number of incident HSV-2 cases was found among Army females ($p<0.01$, Table 4). No other statistically significant differences were found between race, education level, marital status or rank with respect to HSV-1/2 seroprevalence or seroincidence. At the end of four years, the prevalence of HSV-1, HSV-2 and combined infection among males was 42.5%, 6% and 3%, respectively; among females the corresponding prevalence was 57.5%, 16.5% and 8%.

Finally, in the combined sample of 400 personnel, one male and one female subject had prevalent syphilis at the time of service entry. After four years, one male and two female subjects demonstrated newly-acquired treponemal antibody positivity.

Discussion

Consistent with prior studies, we found high rates of HPV and HSV-1/2 infection among active-duty servicemen and servicewomen. Our study adds to a growing knowledge base on STIs in the military and reinforces the need for early and continued prevention efforts in our active-duty population, especially as rates of these infections appear to be higher than in similar age-matched populations.

We found higher seroprevalence and seroincidence of vaccine-preventable serotypes of HPV than have been seen in other observational studies of the U.S. population,⁷ which has clear implications for sexual health within the military and general population. Our study, conducted before the availability of HPV vaccine, demonstrates HPV acquisition rates of 34% during the first ten years of military service, with one-third of new infections among men involving HPV-16 or HPV-18. Presently, HPV vaccination is available to military personnel, but not compulsory, and the HPV vaccine was not specifically recommended for males until 2011, after the period described in this study.¹⁶ Despite the Centers for Disease Control and Prevention's recommendation of universal HPV vaccination,¹⁶ vaccine uptake among males remains low¹⁷, and our data once again underline the urgency of protecting both male and female service members against HPV acquisition. Policies of widespread

vaccination have already yielded tangible benefits: in a study of female military service members, clinically evident genital warts among female service members in the vaccine-eligible age range declined between 2007 and 2010.¹⁸ Based on prior efficacy studies of HPV vaccination on the incidence of male genital warts,¹⁹ a policy of universal male vaccination at entry to service would be expected to produce similar benefits among male servicemembers and is therefore warranted.

Our study also examined the seroprevalence of HSV-1 and HSV-2 in both males and females at service entry and after four years, or a typical tour of duty. Among males, we found a lower prevalence and incidence of HSV-1/2 than was previously reported in a convenience sample of 1,100 military personnel between 1988–2005.²⁰ Here, Page et al reported seroprevalence among 20–29 year-olds for HSV-1 and HSV-2 to be 49% and 7.2%, compared with 33.5% and 1.5% in our 17–27 year-old population. The same study also reported an overall incidence of HSV-1 and HSV-2 of 9.0 and 3.7 per 100 person-years, respectively, as compared with our observed rates of 3.4 and 1.1 per 100 person-years.²⁰ Nonetheless, our findings are consistent with other national data, including the NHANES survey (2005–2010), which estimated seroprevalence of HSV-1 and HSV-2 for males 20 to 29 years of age to be 47% and 6.6%, respectively;^{21,22} at the end of our study, the prevalence of HSV-1 and HSV-2 among males was 43% and 6%, respectively, even as our sample was biased toward younger individuals. Further study is required to better understand the discrepancy in findings from two samples of military personnel and these national estimates.

Likewise, while our reported HSV-1/2 seroprevalence among females is consistent with comparable civilian populations,²¹ the seroincidence was approximately one-half lower than previously cited rates reported by Page et al.²⁰ Nonetheless, our seroconversion rates of 5.5 per 100 person-years for HSV-1 and 3.3 per 100 person-years for HSV-2 are significantly higher than those reported in the large, prospective HerpeVac trial, where the seroconversion rates of HSV-1 and HSV-2 were 2.5 and 1.1 per 100 person-years, respectively.²³ Given that HSV-2 acquisition is reported to be higher among black compared with white women, group differences between cohorts are likely partially responsible for these disparities, as our population was 20% non-Hispanic black, in contrast to 10% for the HERPEVAC cohort.^{21,23} Still, our rates seem especially high, and demographic differences between cohorts would not explain the higher incidence of HSV-1 that we also observed. The large HSV-1/2 seroincidence disparity among females in this study compared to their civilian counterparts, whether a result of risk behavior, differences in social networks or non-sexual transmission (in the case of HSV-1), would also warrant additional research.

Our study has several limitations. Because of our small sample size, we were underpowered to identify statistically significant demographic associations. Clinical data was not obtained, and associated sexual habits and routes of acquisition are unknown. A larger, more comprehensive study could address these issues. Differences in serologic tests between our study and others, particularly those used to detect HSV-1/2 seroconversions, may influence the generalizability of our data and could partially explain discordant findings between our study and others. In addition, the study's sample size was not adequate to estimate the number of cases of a low-prevalence disease such as syphilis. Notwithstanding, the small

numbers of cases would support the current practice against routine screening for syphilis in the military, which was largely abandoned after a 1999 study found it was not cost-effective.²⁴

In closing, our study provides further evidence that HPV and HSV-1/2 continue to be highly prevalent and epidemiologically distinct in the military, highlighting the need for continued prevention efforts. As has often been the case in the treatment of STIs, the military has a unique opportunity to provide leadership and demonstrate the benefits and urgency of recommended, universal male vaccination. Larger epidemiologic surveys and HPV vaccine effectiveness studies are needed to better assess the uptake and effects of universal vaccination.

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Table 1
Prevalence of HPV 6,11,16 and 18 Seropositivity Among Males at Accession by Demographic and Behavioral Characteristics

Demographic/Military Characteristics	Total	HPV 6/11 ^a Seropositivity N(%) ¹	HPV 16/18 ^b Seropositivity N(%) ¹	HPV 6/11, 16/18 ^c Seropositivity N(%) ¹	Univariate Odds Ratio (95% CI)	P-value
All individuals	200	21 (10.5)	10 (5.0)	29 (14.5)		
Age						
17–19	107 (53.5)	11 (10.3)	4 (3.7)	14 (13.1)	Referent	Referent
20–21	39 (19.5)	2 (5.1)	0 (0.0)	2 (5.1)	2.78 (0.60,12.86)	0.189
22–23	35 (17.5)	4 (11.4)	2 (5.7)	6 (17.1)	0.73 (0.26,2.07)	0.550
24–27	19 (9.5)	4 (21.1)	4 (21.1)	7 (36.8)	0.26 (0.09,0.77)	0.015²
Race/ethnicity						
White, non-Hispanic	137 (68.5)	15 (10.9)	9 (6.6)	22 (16.1)	Referent	Referent
Black, non-Hispanic	34 (17.0)	3 (8.8)	0 (0.0)	3 (8.8)	1.98 (0.56,7.04)	0.293
Other	29 (14.5)	3 (10.3)	1 (3.4)	4 (13.8)	1.20 (0.38,3.78)	0.761
Education						
High School or less	168 (84.0)	17 (10.1)	9 (5.4)	24 (14.3)	Referent	Referent
Some College	4 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	-	0.982
College or more	7 (3.5)	1 (14.3)	0 (0.0)	1 (14.3)	1.00 (0.12,8.68)	1
Unknown	21 (10.5)	3 (14.3)	1 (4.8)	4 (19.1)	0.71 (0.22,2.29)	0.564
Marital Status						
Married	14 (7.0)	3 (21.4)	2 (14.3)	5 (35.7)	Referent	Referent
Single	183 (91.5)	16 (8.7)	7 (3.8)	22 (12.0)	4.07 (1.25,13.24)	0.0199²
Divorced/widowed	3 (1.5)	2 (66.7)	1 (33.3)	2 (66.7)	0.28 (0.02,3.88)	0.341
Service Status						
Army	90 (45.0)	13 (14.4)	4 (4.4)	16 (17.8)	Referent	Referent
Marine Corps	34 (17.0)	2 (5.9)	2 (5.9)	4 (11.8)	1.62 (0.50,5.25)	0.42
Navy	76 (38.0)	6 (7.9)	4 (5.3)	9 (11.8)	1.61 (0.67,3.88)	0.2896
Rank Status						
Enlisted	192 (96.0)	20 (10.4)	10 (5.2)	28 (14.6)	Referent	Referent
Office/Warrant	8 (4.0)	1 (12.5)	0 (0.0)	1 (12.5)	1.20 (0.14,10.09)	0.8699

^a HPV serotype 6 or serotype 11 (either one of the serotype was positive or both were positive at accession) were counted as positive in the prevalence rate.

¹Percent of Column Frequency

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HPV serotype 16 or serotype 18 (either one of the serotype was positive or both were positive at accession) were counted as positive in the prevalence rate.
HPV serotype 6, 11, 16 or 18 (either four of the serotypes was positive or any combination of the serotypes were positive at accession) were counted as positive in the prevalence rate.

¹Percent of Column Frequency
¹Percent of Column Frequency
²Statistically significant (p<0.05) in univariate analysis
²Statistically significant (p<0.05) in univariate analysis

Table 2

Incident HPV infection among U.S. servicemen (N=199) after 10 years³ of military service, U.S. Armed Forces, 2010 by Serotype

Sero-Combination	Total 68	One-Serotype 49	Two-Serotype 17	Three-Serotype 2
Type 6	35	35		
Type 11	2	2		
Type 16	6	6		
Type 18	6	6		
Type 6 + 11	6		6	
Type 6 + 16	6		6	
Type 6 + 18	5		5	
Type 6 + 11 + 18	2			2

³_{+/-} 1 year

Baseline demographics and prevalence of HSV-1, HSV-2, and both HSV-1/2 of males (n=200) and females (n=200) at accession.

Table 3

Demographic Characteristics		Total Male (n=200)	Male HSV-1 (%)	Male HSV-2 (%)	Male HSV1/2 (%)	Total Female (n=200)	Female HSV-1 (%)	Female HSV-2 (%)	Female HSV-1/2 (%)
Total			67 (33.5)	3 (1.5)	3 (1.5)		78 (39)	8 (4)	3 (1.5)
Age									
	21–23	101	27 (26.7)	1 (1.0)	1 (1.0)	106	41 (38.7)	5 (4.7)	2 (1.9)
	24–25	42	17 (40.5)	1 (2.4)	1 (2.4)	43	18 (41.9)	1 (2.3)	0 (0.0)
	26–27	37	12 (32.4)	0 (0.0)	0 (0.0)	36	12 (33.3)	1 (2.8)	0 (0.0)
	28–32	20	11 (55.0)	1 (5.0)	1 (5.0)	15	7 (46.7)	1 (6.7)	1 (6.7)
Race									
	White, non-Hispanic	160	50 (31.3)	3 (1.9)	3 (1.9)	122	49 (40.2)	3 (2.5)	1 (0.8)
	Black, non-Hispanic	18	6 (33.3)	0 (0)	0 (0)	39	14 (35.9)	2 (5.1)	0 (0.0)
	Other	22	11 (50.0)	0 (0)	0 (0)	39	15 (38.5)	3 (7.7)	2 (5.1)
Education									
	High School or less	136	47 (34.6)	2 (1.5)	2 (1.5)	124	47 (37.9)	4 (3.2)	0 (0)
	Some College	12	3 (25.0)	0 (0)	0 (0)	26	11 (42.3)	1 (3.8)	1 (3.8)
	College or more	1	1 (100.0)	0 (0)	0 (0)	1	0 (0.0)	0 (0.0)	0 (0)
	Unknown	51	16 (31.4)	1 (2.0)	1 (2.0)	49	20 (40.8)	3 (6.1)	2 (4.1)
Marital Status									
	Married	14	5 (35.7)	0 (0)	0 (0)	10	5 (50.0)	1 (10.0)	1 (10.0)
	Single	184	60 (32.6)	3 (1.6)	3 (1.6)	188	71 (37.8)	7 (3.7)	2 (1.1)
	Divorced/widowed	2	2 (100.0)	0 (0)	0 (0)	2	2 (100.0)	0 (0)	0 (0)
Rank Status									
	Enlisted	190	64 (33.7)	3 (1.6)	3 (1.6)	180	71 (39.4)	8 (4.4)	3 (1.7)
	Office/Warrant	10	3 (30.0)	0 (0)	0 (0)	20	7 (35.0)	0 (0.0)	0 (0)
Service Status									
	Army	90	28 (31.1)	2 (2.2)	2 (2.2)	80	33 (41.3)	3 (3.8)	2 (2.5)
	Marine Corps	57	23 (40.4)	1 (1.8)	1 (1.8)	36	16 (44.4)	4 (11.1)**	0 (0.0)

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Demographic Characteristics		Total Male (n=200)	Male HSV-1 (%)	Male HSV-2 (%)	Male HSV1/2 (%)	Total Female (n=200)	Female HSV-1 (%)	Female HSV-2 (%)	Female HSV-1/2 (%)
Total			67 (33.5)	3 (1.5)	3 (1.5)		78 (39)	8 (4)	3 (1.5)
	Navy	53	16 (30.2)	0 (0)	0 (0)	84	29 (34.5)	1 (1.2)	1 (1.2)
AFQT (IQR)		79	74 (56.86)**	75 (56.82)	75 (56.82)	56	57 (43.72)	62 (54.68)	63 (50.93)

p<0.05

Table 4
Demographic characteristics and Incidence (in 100 person-years) of HSV-1 and HSV-2, cases among males and females after four years.

Demographic Characteristics	Male without HSV-1 at baseline	Incident Male HSV-1 cases	Male without HSV-2 at baseline	Incident Male HSV-2 cases	Female without HSV-1 at baseline	Incident Female HSV-1 cases	Female without HSV-2 at baseline	Incident Female HSV-2 cases
Total	133	18 (3.4)	197	9 (1.1)	122	27 (5.5)	192	25 (3.3)
Age								
	21–23	11 (3.7)	100	8 (2.0)	65	18 (6.9)	101	14 (3.5)
	24–25	5 (5.0)	41	1 (0.6)	25	3 (3.0)	42	7 (4.2)
	26–27	2 (2.0)	37	0 (0.0)	24	5 (5.2)	35	1 (0.7)
	28–32	0 (0.0)	19	0 (0.0)	8	1 (3.1)	14	3 (5.4)
Race								
	White, non-Hispanic	15 (3.4)	157	7 (1.1)	73	16 (5.5)	119	13 (2.7)
	Black, non-Hispanic	1 (2.1)	18	2 (2.8)	25	4 (4.0)	37	9 (6.1)
	Other	2 (4.5)	22	0 (0.0)	24	7 (7.3)	36	3 (2.1)
Education								
	High School or less	12 (3.4)	134	7 (1.3)	77	16 (5.2)	120	13 (2.7)
	Some College	1 (2.8)	12	0 (0.0)	15	3 (5.0)	25	1 (1.0)
	College or more	0 (0.0)	1	0 (0.0)	1	0 (0.0)	1	0 (0.0)
	Unknown	5 (3.6)	50	2 (1.0)	29	8 (6.9)	46	11 (1.6.0)
Marital Status								
	Married	2 (5.6)	14	0 (0.0)	5	2 (11.0)	9	2 (5.6)
	Single	16 (3.2)	181	9 (1.2)	117	25 (5.3)	181	22 (3.0)
	Divorced/widowed	0 (0)	2	0 (0.0)	0	0 (0)	2	1 (12.5)
Rank Status								
	Enlisted	18 (3.6)	187	9 (1.2)	109	26 (6.0)	172	24 (3.5)
	Office/Warrant	0 (0.0)	10	0 (0.0)	13	1 (1.9)	20	1 (1.3)
Service Status								
	Army	6 (2.4)	88	3 (0.9)	47	9 (4.8)	77	17 (5.5)***
	Marine Corps	5 (3.7)	56	2 (0.9)	20	4 (5.0)	32	2 (1.6)

Demographic Characteristics	Male without HSV-1 at baseline	Incident Male HSV-1 cases	Male without HSV-2 at baseline	Incident Male HSV-2 cases	Female without HSV-1 at baseline	Incident Female HSV-1 cases	Female without HSV-2 at baseline	Incident Female HSV-2 cases
Total	133	18 (3.4)	197	9 (1.1)	122	27 (5.5)	192	25 (3.3)
Navy	37 (27.8)	7 (4.7)	53	4 (1.9)	55	14 (6.4)	83	6 (1.8)
AFQT	64 (50.80)	65 (50.79)	61 (45.79)	59 (48.70)	56 (45.71)	60 (44.71)	56 (44.73)	56 (45.71)

**
p<0.01