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Factors Associated with Adherence to Factor Replacement In the Hemophilia Population

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2015

Abstract

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Background: Hemophilia is a bleeding disorder managed with factor replacement products though adherence is complex. Health literacy (HL) is the degree to which one can understand health information and make health decisions. Numeracy deals with probability and numerical concepts. The primary aim was to see if there was an association between poor HL and numeracy in patients with hemophilia (PWH) and decreased adherence to factor replacement therapy. Other aims include the investigation of associations between other factors such as physician trust, quality of life, and depression history and adherence to factor replacement therapy.

Methods: In a cross-sectional study, adult PWH were recruited during the Hemophilia Treatment Center (HTC) visit. They completed questionnaires to obtain adherence, HL, and numeracy measurements, as well as other independent variables. Multiple regression was performed to determine the association between poor HL and numeracy with adherence to factor replacement therapy while adjusting for possible confounders.

Results: All were men (n=99); 91% had hemophilia A and 78% had severe disease. Age ranged from 18 to 62, with a mean age 33 (SD 18). Most were white (69%). Mean duration followed at HTC was 16.0 years (SD 11). Depression history was reported in 21%. Most (95%) had high HL; but only 23% were numerate. The mean adherence scores were 45.6 (SD 18) and 51.0 (SD 15) depending on regimen prescribed. On multivariable analysis, HL score and numerate status were not significantly associated with adherence. Being on any chronic medication, longer duration seen at HTC, higher physician trust, and better quality of life were associated with higher adherence. Depression history was associated with lower adherence.

Conclusion: In this study population, numeracy was not associated with adherence. A large majority of the PWH in our study were health literate. This study showed being on any chronic medication, longer duration followed at the HTC, higher physician trust, better quality of life, and no depression history were associated with better adherence. These factors provide a better understanding of characteristics that influence adherence and may prove important for optimizing the care of PWH.

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INTRODUCTION

Hemophilia is a chronic bleeding disorder characterized by a deficiency in coagulation factor VIII or IX. Without treatment, the most common complication is bleeding into joints, also known as hemarthrosis, which can lead to irreversible functional impairment and chronic pain. With treatment aimed at replacing the missing clotting factor, bleeding episodes can be minimized and even prevented, which ultimately decreases pain and morbidity and mortality in patients with hemophilia and increases quality of life and physical activity (1, 2).

Factor replacement regimens can be prescribed as either prophylaxis or on-demand. The prophylactic regimen is preventative and is administered as regular infusions of factor concentrates 2-3 times a week (3). On-demand factor replacement is when the patient only treats with factor replacement at the time of a bleed. For patients with hemophilia, adherence to factor replacement therapy is important although rather complex. Factor replacement therapy requires administering factor replacement intravenously, maintaining infusion records, planning ahead to ensure adequate factor supplies at home, understanding different medication doses, and communicating with treatment center for bleeds and upcoming procedures. Determinants of adherence to medication regimens for hemophilia, similar to other chronic conditions, can be multifactorial. In chronic illnesses, in addition to reporting on demographic, socioeconomic, and patient-related factors that affect adherence. Some studies looked at health literacy and numeracy and demonstrated low health literacy and low numeracy were barriers to adherence to medication regimens in chronic medical conditions.

Health literacy is the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions (4). Numeracy is the ability to handle basic probability and numerical concepts like estimation and problem solving (5). In the current study, adherence to factor replacement in the hemophilia population and characteristics that may influence adherence were examined; with particular focus on a patient's health literacy and numeracy as predictors of adherence to factor replacement. The aim was to determine if poor health literacy and poor numeracy in patients with moderate or severe hemophilia was associated with decreased adherence to factor replacement therapy. The secondary aim was to determine the association between other demographic, socioeconomic, and psychosocial measurements and adherence to factor replacement therapy.

BACKGROUND

Hemophilia is a chronic disorder due to the deficiency of a clotting factor. Hemophilia A, a deficiency in factor (F) VIII, affects 1 in 5,000 male births; hemophilia B, a deficiency in FIX, affects 1 in 25,000 male births (6). The deficient protein in hemophilia can be prescribed to prevent and to treat bleeding complications. Untreated patients can develop bleeding complications, which can vary from bleeding into the joints resulting in chronic disability and pain to having a life-threatening intracranial bleeding. Therefore, understanding the need for factor replacement and adherence to the regimen established by the patient and the hemophilia treatment center (HTC) are of utmost importance. Factor replacement therapy can be prescribed as either preventative through a prophylactic regimen or as episodic through an on-demand regimen for treatment at time of a bleed. Regardless of prophylactic treatment or on-demand treatment, adherence to replacement therapy is required in order to prevent or decrease the amount of bleeding and, thereby, decrease the degree of hemophilic arthropathy. However, in patients with hemophilia, adherence to factor replacement regimens can be complicated and costly. Adherence to a medication regimen is defined as "the extent to which patients take medications as prescribed by their health care providers" (7). To be adherent, patients must rest the painful joint, treat with factor replacement promptly, obtain intravenous access, maintain calendars of infusions, plan ahead to ensure adequate amounts of factor at home, understand different dosing of medication for the severity of a bleed, communicate with treatment center, and attend annual HTC visits.

Although adherence to factor replacement regimens is important, some patients do not adhere to factor replacement therapy. Studies examining the barriers to adherence to factor replacement in the adult hemophilia population have been limited. In one study with 22 participants, time constraints, a non-modifiable predictor, was identified as a barrier to adherence (8). More recently, a systematic review resulted that motivators for high adherence included experience of symptoms, positive belief of necessity of treatment and a good relationship with the health care provider (9). Barriers to adherence to factor replacement included absence of symptoms and increasing age.

Previous studies looking at the influences on adherence to medication regimen for other chronic conditions have shown them to be multifactorial. Patients on oral medications for heart failure and anti-cancer regimens had increased adherence with higher education (10, 11). Older age was also increased adherence in those patients with heart failure and Parkinson’s disease (10, 12). In patients with Parkinson’s disease, it was shown that ethnic minorities are less adherent to their oral regimens (12). Less adherence was also seen in those patients taking other medications in patients with Parkinson’s disease and oral anti-cancer therapy (11, 12). Financial status (11, 12) and gender (10, 11) did not affect adherence. In other chronic medical conditions, health literacy and numeracy were also identified as barriers to adherence to treatment regimens.

Health literacy includes basic reading (print literacy), listening and speaking (oral literacy), cultural knowledge, and numerical tasks (numeracy), which are required to function in the health care environment. Health literacy is an immense problem in the United States (US). In 2006, the US Department of Education published the National Assessment of Adult Literacy, which measured health literacy over 19,000 US adults; about 36% were identified as having limited health literacy and only 12% were considered proficient(13). Poor health literacy has been reported in older individuals (14).

In patients with the human immunodeficiency virus (HIV), low health literacy was associated with poor adherence to antiretroviral therapy (15) and, in turn, poor control of their disease. In patients on warfarin for the management of atrial fibrillation or treatment of venous thromboembolism, low health literacy and low numeracy has been associated with poor adherence to warfarin intake resulting in not being able to maintain the target range resulting in poor anticoagulation control (16).

Numeracy, an under-recognized component of health literacy, is further defined as the ability to handle basic probability and numerical concepts including computation, estimation, logic, and problem solving (5). In addition to not maintaining adequate anticoagulation for patients on warfarin, Low numeracy had been shown to be strongly associated with female patients not obtaining screening mammography because they did not understand the benefit (5).

Patients with poor health literacy and numeracy have problems including reading medication labels, naming their medications, describing the medication indications, understanding dosing schedules, comprehending educational brochures, and have poor understanding of their condition and its management (4, 17). Health literacy and numeracy are of utmost importance in the health care system as there is great emphasis placed on self-management and self-advocacy. Poor health literacy, and more particularly poor numeracy, can be a barrier to chronic disease care.

Although studied in other chronic disease, health literacy and numeracy has not been studied in patients with hemophilia. Health literacy is needed in patients with hemophilia to understand the dosing schedule if they are prescribed a prophylactic regimen; these schedules can vary from every other day infusions to two to three times a week. Numeracy is needed to understand the dosing required to treat a mild bleeding episode or a major bleed episode since these doses do differ. Factor replacement therapy can be supplied as a single dose or vials that sum up to a single dose. Because factor replacement products are not stocked at local pharmacy and must be ordered through specialty pharmacies that only operate and deliver during work days, numeracy skills are important to understand how many treatment doses remain given the number of vials available at home; patients need to know when to order new shipments in preparation for weekends or holidays. Both health literacy and numeracy skills are needed to prevent adverse health outcomes. Therefore we hypothesized that both poor health literacy and numeracy in patients with moderate or severe hemophilia are associated with decreased adherence to treatment with factor replacement products. Also, we hypothesized that other variables such as age, quality of life, physician trust, duration of time followed at the HTC (years), use of chronic medications and diagnosis of past or current depression in patients with moderate or severe hemophilia are associated with decreased adherence to treatment with factor replacement products.

METHODS

Characteristics of the study population

In this cross-sectional study, after the Emory University Institutional Review Board approved the study, patients scheduled to be seen at Emory/Children's Healthcare of Atlanta Hemophilia Treatment Center (HTC) between November 1st, 2012 and January 2nd, 2014 were pre-screened for age and severity of hemophilia. Patients who were 18 years and older with either moderate or severe hemophilia A or B were considered potentially eligible and approached in clinic to determine eligibility. Additional eligibility criteria included current use of FVIII or FIX replacement therapy. If using an on-demand regimen, then these subjects must have had 3 or more hemarthroses in the past year. As a result of limited language availability of several research tools used in this study, subjects were required to have been English speaking individuals who were comfortable with reading English. Lastly, they must have had someone in the household with the ability to infuse factor product; having the ability for someone in the household to infuse the factor product would allow the patient to treat more readily rather than having to wait for the home health care nurse to be come to the house or rather than going to the emergency department to gain intravenous access. Anyone not meeting all the previously mentioned criteria, patients with mild hemophilia, and those who treated with bypass therapy were excluded.

Measurements

Sources of Data:

Dependent (outcome measure) variable: The primary outcome measure is adherence to factor replacement therapy using the self-reported Validated Hemophilia

Regimen Treatment Adherence Scale (VERITAS)-Pro and VERITAS-PRN (3, 18). Both are validated scales of adherence developed by Indiana University. The VERITAS-Pro scale was used in subjects on prophylaxis regimens; the VERITAS-PRN scale was used with those who used on-demand treatment for episodic bleeding episodes. Both self-reported questionnaires consisted of 24 questions on six subscales. The six subscales of the VERITAS-Pro were Time, Dose, Plan, Remember, Skip, and Communicate. The six subscales of the VERITAS-PRN were Treat, Time, Dose, Plan, Remember, and Communicate. Within each subscale, there were 4 items; each item had a Likert scale with 5 levels of "Always", "Often", "Sometimes", "Rarely", and "Never". The range for the total score was from 24 to 120, where the lower the score, the higher the adherence. The VERITAS-Pro has validated cut-off scores for adherent (total score ≤ 57) and non-adherent (total score > 57). The six subscale cut-off scores for adherent are ≤ 11 for Time, ≤7 for Dose, ≤9 for Plan, ≤11 for Remember, ≤11 for Skip, and ≤10 for Communication. There are no determined cut-off scores for the VERITAS-PRN.

Independent Variables: Primary independent variables measured health literacy and numeracy. The shortened Test of Functional Health Literacy in Adults (s-TOFHLA) and the Schwartz-Woloshin Numeracy Test were administered in an interview format to ensure these were administered properly and to ensure there was no aid from others in the room or from electronic devices to complete the questionnaires. Other covariates were collected to examine additional associations with adherence and identify those confounding the association between adherence and health literacy and numeracy. The remainder of the questionnaires collected was left with the participant in the room to be completed during the visit.

Health Literacy: The s-TOFHLA, a reliable and validated instrument, was used to assess a patient's health literacy level (19). This tool is used to measure functional health literacy using actual health-related materials which included an x-ray preparation and Medicaid rights and responsibilities. The s-TOFHLA has 2 prose passages with a total of 36 reading comprehension items. The reading comprehension uses the modified Cloze procedure, where every fifth to seventh word in a passage is omitted, and the patient has to select the correct answer out of 4 multiple choice options provided. The total score ranged from 0 to 36; a score $\geq$ 23 was considered health literate; any total score <23 was classified as not health literate.

Numeracy: The original (3-item) scale created by Schwartz & Woloshin was used and administered under observation to assess the patient's ability to understand and use numeric information (5). These 3 items used fill-in-the-blank responses. To be considered numerate, one must answer all 3 questions correctly.

Wake Forest Physician Trust Scale: This is a 10-item uni-dimensional scale (20). The measurement of scores of trust in physicians ranged from 1 to 5 for each item. The total score of ranged from 10 to 50 with a higher score indicating greater physician trust.

Health-related quality of life: Both disease-specific and general health related quality of life tools were used. Hemophilia-specific health-related quality of life: The Haem-A-QoL is a validated tool that looks specifically at how hemophilia affects the quality of life in adults with hemophilia (21). This consisted of 46 items divided into 10 sections and a total score. The 10 sections included “physical health”, “feelings”, “view of yourself”, “sport and leisure”, “work and school”, “dealing with haemophilia”, “treatment”, “future”, “family planning”, “partnership and sexuality”. The total score ranged from 33-230 with a lower score indicating a higher quality of life. General health-related quality of life: The SF-12 is a 12-item questionnaire that was used to assess the patient's view on their own general health status and how their health impacts their usual activities (22). The scores were divided into a physical health composite score and a mental health composite score which are computed using the score of the 12 questions and range from 0 to 100, where a zero score indicates the lowest level of health measured by the scale and 100 indicates the highest level of health. Both physical and mental health composite scales combine the 12 items in such a way that they compare to a national norm with a mean score of 50.0 and a standard deviation of 10.0. A positive difference between a person's score and the mean score means the person is healthier than average; whereas, a negative score means a person is less healthy than average.

General Self-Efficacy: Self-efficacy is the extent of one's belief in one's own ability to complete tasks and achieve goals. The General Self-Efficacy questionnaire is a 10-item scale used to assess a general sense of perceived self-efficacy with predicting how well patients cope with daily hassles and how they adapt to all kinds of stressful life events (23). The scores of self-efficacy ranged from 1 to 4 for each item. The total score of ranged from 10 to 40 with a higher score indicating greater self-efficacy.

Demographic and Socioeconomic information: Information of race, ethnicity, gender, age, education level (no schooling, completed kindergarten - 8th grade, completed 9th – 12th grade but no diploma, high school diploma, GED, completed some college but no degree, associate's degree, bachelor's degree, master's degree, post-graduate degree, doctorate degree), income level ($0-14,999; $15,000-24,999; $25,000-34,999; $35,000-49,999; $50,000-$74,999; $75,000-99,999; or >$100,000), access to a car, employment status (student, working full time, working part time, unemployed, disabled, and retired), and insurance status were collected on the self-reported questionnaire.

Health information: Health information including diagnosis (hemophilia A or B), severity of disease (moderate or severe), presence or absence of HIV infection, and presence or absence of Hepatitis C (HCV) antibody was obtained from review of the electronic medical records. Additionally, subjects self-reported current or past diagnosis of depression, presence of any joint with greater than 20 bleeds during a lifetime, and whether the patient takes other medication(s) chronically.

Sample-size and power

The pre-enrollment target was 90 individuals to have 90% power to detect an R^2 of 0.30 attributed to the 2 independent variables of interest (health literacy and numeracy) plus 5 additional independent variables. There was an assumption that about half of the subjects would not be health literate and numerate.

Statistical analysis plan

Descriptive statistics (mean for non-skewed variables and median for skewed variables) were calculated for each variable of demographic measures, socioeconomic measures, hemophilia-related measures, other health measures, psychosocial measures, and literacy measures. Education level was dichotomized into those that did not graduate college and those that did complete college. Income level was dichotomized at < and ≥ $50,000 based on the median annual income in the United States of $51,000 in 2013 (24). Bivariable associations between the continuous outcome adherence and each predictor variable were assessed using simple linear regression. Collinearity was assessed by calculating pairwise Pearson correlation coefficients between variables including health literacy score, numerate status, the Wake Forest Physician Trust Scale, the Haem-A-QoL score, the physical and mental component score of the SF-12, the General Self-efficacy score, length of time at this HTC, education level, and income level. To ensure that the same effect was not measured by more than one variable, any pairwise Pearson correlation coefficient > 0.4, only one variable of the pair was included in the multivariable linear regression model.

Multivariable analysis was performed using multivariable linear regression. In all models, adherence as measured by the VERITAS score was the outcome variable. In the first model, health literacy and numerate status were the primary exposure variables of interest. Additional variables were evaluated for confounding and included in the model if they demonstrated confounding on the association between health literacy or numeracy and adherence. Variables selected as possible confounders included those variables that were found to be associated with health literacy or numeracy on bivariable analysis (p-value<0.10) as well as those considered to be possible confounders based on the literature (age, race, education, and household income). Variables that led to a 10% change in the regression coefficient associated with health literacy or numeracy. Interaction was evaluated between health literacy and the variables of age, race, depression, income level, and education level; none of these combinations showed any effect modification. Interaction was evaluated between numeracy and the variables of age, race, income level, education level, and use of chronic medications; none of these combinations revealed any effect modification either.

In the second model, variables that were significant or approaching significance (P-value <0.25) in simple linear regression were included as exposure variables. The remaining variables were individually included in the model to assess confounding of the association between exposure variables and adherence. Interaction between use of any chronic medication and the variables of age, race, disease severity, and income level; depression and the variables of age, race, severity, income level, education level, and employment status; duration seen at the HTC and the variables disease severity, treatment regimen, HIV infection, and HCV antibody; physician trust and the variables of age, race, HIV infection, HCV antibody, income level, education level, and duration seen at the HTC; and the quality of life (measured by the Haem-A-QoL) and the variables of age, race, disease severity, treatment regimen, HIV infection, HCV antibody, income level, employment status were also checked. All analyses were done using SAS version 9.3 (SAS Institute, Cary, North Carolina). P-values <0.05 were considered statistically significant.

RESULTS

Demographic and health characteristics

One-hundred and sixty-eight patients were pre-screened for age and hemophilia severity prior to clinic visit; 19 were did not show up for the scheduled clinic appointment and 20 were not approached due to time restrictions. This left 129 screened patients who were approached during clinic; 21 of these patients did not meet all the inclusion criteria and 9 who were eligible declined to participate. Data was collected from 99 adult males; 91 subjects completed all parts of the study (Table 1). Among the 8 subjects with missing information, the Wake Forest physician trust questionnaire, both quality of life measurements, the General Self-Efficacy score, income level, employment status, insurance status, and self-reported health information were missing. The mean age of the subjects was 33 years old and ranged from 18 to 62 years old. The majority of the subjects were white (69%) and non-Hispanic (94%). Most had hemophilia A (91%) and severe disease (78%) with the majority with at least one joint with greater than 20 bleeds during their lifetime (97%). HIV infection was noted in 26%, and HCV antibody positive in 59%; depression history was reported in 21%; 49% infused replacement factor prophylactically. The proportion of subjects on any chronic medications not including factor replacement was 45%. The mean length of time followed at the HTC was 16 years (SD 11). The mean VERITAS-Pro was 45 (SD 18) and the mean VERITAS-PRN was 51 (SD 15) with a lower score indicating greater adherence.

Socioeconomic/Psychosocial/Health literacy measures

A substantial proportion of participants (42%) reported their annual household income was $0-$24,999. About half of the participants reported that the highest level of education was a bachelor's degree or higher. Thirty-five percent reported they were currently unemployed; 78% owned a car. Most of the participants reported high physician trust (mean score 42.6 [SD 6.6]) and high general self-efficacy (mean score 34.3 [SD 4.2]). The mean Haem-A-QoL score was 97.3 (SD 33.2) with 33 representing the highest quality of life. Compared to the general population, the average physical functioning was lower than most (mean SF-12 physical component score 45.1 [SD 11.7]); but emotionally, the patients were bothered less than most (mean SF-12 mental component score was 54.5 [SD 8.6]). Most of the study population (95%) had adequate health literacy; but only 23% were numerate.

Characteristics associated with adherence

On bivariable analysis, the outcome of interest, adherence, was associated with treatment regimen, duration followed at the HTC, history of depression diagnosis, education level, physician trust score, general self-efficacy, and quality of life ($p \leq 0.10$) (Table 2). To evaluate variables that are potentially associated with health literacy and numeracy in this cohort and therefore potential confounders on the association of health literacy and numeracy and adherence, bivariable associations were evaluated using simple linear regression. Both health literacy and numeracy were associated with annual household income, education level, and quality of life ($p\leq 0.10$) (Table 3 and 4). Health literacy alone was associated with race, HIV status, employment status, owning a car, and general self-efficacy ($p \leq 0.10$) (Table 3). Numeracy alone was associated with duration followed at the HTC, the use of any chronic medication and physician trust score, ($p \leq 0.10$) (Table 4).

The variable of Haem-A-QoL was correlated with physical health component score of the SF-12 (correlation coefficient -0.6) and general self-efficacy (correlation coefficient -0.4); and history of depression diagnosis was with the mental health component score of the SF-12 (correlation coefficient -0.5). Of these correlated variables, Haem-A-QoL and history of depression diagnosis were included in the models. In the multivariable linear regression model for the primary exposure variables of interests (health literacy and numeracy), adherence was not significantly associated with health literacy score and numerate status (Table 5) after adjusting for the confounders including duration followed at the HTC, physician trust, Haem-A-QoL, and highest education level.

To evaluate the association of other clinical, demographic and health-related characteristics and their association with adherence, a second multivariable linear regression model was created and included variables that were considered approaching significance (P-value <0.25) on bivariable analysis with adherence (Table 6). After adjusting for treatment regimen, being on any chronic medication, longer duration followed at HTC, higher physician trust, and better quality of life were significantly associated with higher adherence (Table 6).

The second multivariable regression model included variables that were associated with adherence on bivariable analysis. We kept in the variables that were approaching significance with p-value<0.25 to build the model to see what were significant predictors to adherence in this hemophilia population. Some of these variables such as duration followed at the HTC, physician trust, and quality of life were confounders in the first model but were not confounders in the second model; this second model also included the use of chronic medications and the history of depression diagnosis. Each of these variables was assessed for confounding and only treatment regimen was found to be confounding. We also assessed for interaction as well with no effect modification noted. After adjusting for treatment type, having a history of depression diagnosis was significantly associated with lower adherence. Being on any chronic medication, longer length of time seen at the HTC, higher physician trust, and better quality of life were significantly associated with better adherence

A self-reported current or past diagnosis of depression was significantly associated with lower adherence. Subjects with history of depression diagnosis had lower adherence and would expect to have a 7 points higher VERITAS score than those not without a history of depression diagnosis. Those on chronic medications, followed longer here at the HTC, who had higher physician trust, and who had higher quality of life were all associated with better adherence. Those on any chronic medication had higher adherence and would expect to have a 6 points lower VERITAS score than those not on any chronic medication. Those who had been followed at this HTC longer had higher adherence and would expect to have a 3 points lower VERITAS score for every 10 years followed. For every 10 points higher on the physician trust scale, one would expect about 5 points lower on the VERITAS score. Since the Haem-A-QoL score is directly proportional to the VERITAS adherence score, for every 10 points decrease in the Haem-A-QoL score, one would expect about 1.3 points lower of the VERITAS score. This second model overall accounted for a moderate proportion of the variability of adherence between subjects (adjusted $R^2 = 0.296$).

DISCUSSION

In this study, we found that the exposure variable numeracy is not associated with adherence to factor replacement in the hemophilia population (*P-value* 0.89). With the majority of subjects with adequate health literacy scores, we are not able to make further conclusions in regards to the association of health literacy and adherence to factor replacement. In the second model, after adjusting for treatment type, having a history of depression diagnosis is significantly associated with lower adherence to factor replacement in the hemophilia population. Being on any chronic medication, longer duration followed at the HTC, higher physician trust, and better quality of life are significantly associated with better adherence.

The study contributes observational descriptive data about health literacy and numeracy in a population not previously reported. At the inception of this study, there were no description of health literacy and numeracy in any of those individuals with hematological disorders. Recently, an abstract from Shook, et al., was presented at the 2013 annual American Society of Hematology meeting about health literacy in patients with sickle cell disease. This area remains a vastly underreported and understudied area of research for those with bleeding disorders. To our knowledge, the health literacy and numerate status of subjects with hemophilia have never been reported.

Previous studies that have looked at patients with chronic medical conditions and medication adherence showed that higher education and older age was associated with higher adherence (10-12). In this study, education level and age were not significant and were not associated with adherence to factor replacement. In patients with Parkinson's disease and those on an oral anti-cancer therapy, those taking other medications were associated with less adherence (11); whereas, our study demonstrated that the use of any chronic medication was associated with adherence to factor replacement. This may be secondary to the type of medication each subject was taking; there is no information about the exact medication that the subjects were taking. Previous studies in patients with hemophilia did report that a good relationship with the health care provider was associated with improved adherence (9); our study demonstrated that high physician trust was associated with better adherence. Although physician trust can be different than having a good relationship with the health care provider, there is some overlap in these concepts.

Although there was not much variability in the health literacy scores of this single-center study population, there is ample opportunity to understand the health literacy of the general hemophilia population. In the field of health literacy, there are several different tools to measure this in the health care setting. Such tools can include the s-TOFHLA, TOFHLA (19), Rapid Estimate of Adolescent Literacy in Medicine (REALM) (25), and The Newest Vital Sign (NVS) (26). Each tool has its advantages and disadvantages but there is no one universally accepted tool for the measurement of health literacy. The s-TOFHLA and TOFHLA can be lengthy and requires 7-10 minutes and 18-22 minutes, respectively, to administer but is available in English and Spanish. The REALM can be administered in less than 3 minutes but is only available in English. The NVS requires 3 minutes to administer and is available in English and Spanish but must be orally administered and is the newest tool created and validated.

The largest limitation to this analysis was that the majority of the study population had adequate health literacy. Due to the limited number of study participants with inadequate and marginal health literacy, there is no conclusion that can be made about the association of health literacy and adherence to factor replacement in the hemophilia population. This may be because of the young average age of the study population. The literature previously describing low health literacy associated with poor adherence in diabetic patients also used the s-TOFHLA to test health literacy but the participants with diabetes had an average age of 58 (17). Another possible reason is that our enrollment was limited to those who made it to their scheduled HTC appointments and were sufficiently on time to allow completion of study questionnaires. We did not seek out those that did not show up to their scheduled clinic visits. However, there was no difference in age, diagnosis, race, ethnicity, and treatment regimen between those who participated and those who were scheduled for clinic and did not show and those that declined to participate. Another limitation is due to the limited validated tools in other languages. We limited our enrollment to only those who were comfortable with reading and speaking English.

To continue and build on the information gained from this study, we can continue to explore health literacy amongst patients with bleeding disorders by developing a plan for a multi-centered cross-sectional study to measure health literacy that is large enough to provide an estimate of the proportion of persons with low health literacy. This would inform whether future larger studies to evaluate the impact of health literacy on adherence or other outcomes are feasible

Since physician trust is associated with adherence to factor replacement in the hemophilia population, another next step is developing a pilot prospective study to test an intervention to improve physician trust and assess its impact on adherence to factor replacement therapy. Exposures that have been identified to have an association with physician trust are improved interpersonal aspects of care (27) but no exposures associated with physician trust have been identified in the hemophilia population.

Our study provides empirical evidence that numeracy is not associated with adherence to factor replacement in the hemophilia population. As research continues to grow to improve the care of patients with hemophilia, several modifiable exposures have been identified in this study such as increasing physician trust and early diagnosis of depression. This study provides insight into the health literacy of the hemophilia population at a single center but this information cannot be generalized and should be further investigated to accurately represent this population.

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Table 1: Subject Characteristics (n=99)

Characteristic	n (%) or mean (SD)	
Demographics		
Age (years)	33	(18)
Male Gender	99	(100%)
Race (n=91)		
White	63	(69%)
Black	24	(27%)
Asian	3	(3%)
Hispanic Ethnicity (n=91)	5	(6%)
Hemophilia Measures		
Hemophilia A	90	(91%)
Severe Disease	77	(78%)
Prophylaxis Regimen	49	(49%)
Length of time seen in Emory HTC (years) (n=91)	16	(11)
Any target joint(s) (n=91)	88	(97%)
VERITAS-Pro Score (n=45) (24-120)	45	(18)
Adherent if Pro Score ≤ 57	36	(80%)
VERITAS-PRN Score (n=46) (24-120)	51	(15)
Other Health Measures		
HIV Antibody Positive (n=91)	24	(26%)
HCV Antibody Positive (n=91)	54	(59%)
Any chronic medication use (n=91)	41	(45%)
Depression History (n=91)	19	(21%)
Socioeconomic Measures		
Income Level (n=91)		
$0 - $24,999	38	(42%)
$25K - $49,999	17	(19%)
$50K - $99,999	25	(27%)
$100K or more	11	(12%)
Highest Education (n=91)		
Less than a high school diploma	8	(9%)
High school diploma/GED	25	(27%)
Completed some college and/or associate's degree	25	(27%)
Bachelor's degree	23	(26%)
Graduate degree	10	(11%)
Unemployed currently (n=91)	32	(35%)
Owns a car (n=91)	71	(78%)
Psychosocial Measures		
WFPTS Score (n=91) (10-50)	42.6	(6.6)
GSE Score (n=91) (10-40)	34.3	(4.2)
Haem-A-QoL Score (n=91) (33-230)	97.3	(33.2)
SF-12 Physical Component Score (n=91)	45.1	(11.7)
SF-12 Mental Component Score (n=91)	54.5	(8.6)

Literacy Measures		
s-TOFHLA Score (n=98) (0-36)	35*	(1)**
Inadequate (0-16)	2	(2%)
Marginal (17-22)	3	(3%)
Adequate (23-36)	86	(95%)
Correct Answers for the SW Numeracy Questions (n=98)		
0	13	(13%)
1	27	(28%)
2	35	(36%)
3	23	(23%)

*. Median; **. Interquartile Range

SD: Standard Deviation; HTC: Hemophilia Treatment Center; VERITAS-Pro: validated hemophilia regimen treatment adherence scale (on prophylaxis); VERITAS-PRN: validated hemophilia regimen treatment adherence scale (for those who infuse only when there is a bleed); HIV: Human Immunodeficiency Virus; HCV: Hepatitis C Virus; GED: General Education Development; WFPTS: Wake Forest Physician Trust Scale; GSE: General Self-Efficacy; s-TOFHLA: shortened Test of Functional Health Literacy in Adults; SW: Schwartz-Woloshin

Table 2: Bivariable Linear Regression Evaluating the Association Between Adherence and Clinical and Demographic Predictors (n=91)[1]

Predictor	**Beta Coefficient**	**Standard Error**	**p-value**
Demographics			
Age	-0.05	0.11	0.65
White race (ref: all other)	-0.56	2.79	0.84
Hispanic Ethnicity (ref: non-Hispanic)	-1.62	5.65	0.78
Hemophilia Measures			
Hemophilia A (ref: B)	0.86	4.31	0.84
Severe Disease (ref: moderate)	-0.58	3.01	0.84
Prophylaxis Regimen (ref: on-demand)	-5.49	2.51	0.03
Length of Time at HTC (years)	-0.20	0.12	0.09
Any target joints (ref: none)	4.13	7.21	0.57
Other Health Measures			
HIV Positive (ref: HIV negative)	-0.67	2.92	0.82
HCV Positive (ref: HCV negative)	-0.95	2.62	0.72
On chronic medication(s) (ref: none)	-3.17	2.57	0.22
Depression History (ref: none)	6.30	3.10	0.04
Socioeconomic Measures			
Annual Income ≥ $50,000 (ref: ≤ $50,000)	-2.15	2.63	0.41
Completed undergrad or higher (ref: no undergrad)	-4.80	2.63	0.07
Unemployed/Disabled (ref: employed/retired)	2.43	2.69	0.37
Owns car (ref: no car)	-1.95	3.11	0.53
Psychosocial Measures			
WFPTS Score	-0.72	0.18	<0.01
GSE Score	-0.70	0.30	0.02
Haem-A-QoL score	0.13	0.037	<0.01
PCS	-0.17	0.11	0.11
MCS	-0.45	0.14	<0.01
Literacy Measures			
s-TOHFLA score	-0.28	0.24	0.24
Numerate (ref: numeracy < 3)	0.40	3.01	0.89

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[1]: Results from simple linear regression

HTC: Hemophilia Treatment Center; HIV: Human Immunodeficiency Virus; HCV: Hepatitis C Virus; WFPTS: Wake Forest Physician Trust Scale; GSE: General Self-Efficacy; PCS: Physical Component Score of SF-12; MCS: Mental Component Score of SF-12; s-TOFHLA: shortened Test of Functional Health Literacy in Adults

Table 3: Bivariable Linear Regression Evaluating the Association of Health Literacy with Clinical and Demographic Variables (n=91)[1]

Predictor	Beta Coefficient	Standard Error	p-value
Demographics			
Age	-0.07	0.05	0.16
White race (ref: all other)	3.57	1.17	<0.01
Hispanic Ethnicity (ref: non-Hispanic)	1.67	2.49	0.50
Hemophilia Measures			
Hemophilia A (ref: B)	-1.11	1.90	0.56
Severe Disease (ref: moderate)	-0.07	1.33	0.96
Prophylaxis Regimen (ref: on-demand)	0.49	1.14	0.67
Length of Time at HTC (years)	0.07	0.05	0.20
Any target joints (ref: none)	-0.81	3.18	0.80
Other Health Measures			
HIV Positive (ref: HIV negative)	-2.51	1.26	0.05
HCV Positive (ref: HCV negative)	-0.77	1.15	0.51
On chronic medication(s) (ref: none)	-0.31	1.14	0.79
Depression History (ref: none)	-1.07	1.39	0.44
Socioeconomic Measures			
Annual Income ≥ $50,000 (ref: ≤ $50,000)	2.26	1.14	0.05
Completed undergrad or higher (ref: no undergrad)	1.56	1.17	0.19
Unemployed/Disabled (ref: employed/retired)	-2.46	1.16	0.04
Owns car (ref: no car)	2.97	1.34	0.03
Psychosocial Measures			
WFPTS Score	-0.03	0.09	0.73
GSE Score	0.26	0.13	0.05
Haem-A-QoL score	-0.03	0.02	0.15
PCS	0.13	0.05	<0.01
MCS	0.03	0.07	0.71
Literacy Measures			
Numerate	2.02	1.27	0.12

[1]: Results from simple linear regression

HTC: Hemophilia Treatment Center; HIV: Human Immunodeficiency Virus; HCV: Hepatitis C Virus; WFPTS: Wake Forest Physician Trust Scale; GSE: General Self-Efficacy; PCS: Physical Component Score of SF-12; MCS: Mental Component Score of SF-12.

Table 4: Bivariable Logistic Regression Evaluating the Association of Numerate Status with Clinical and Demographic Variables (n=91)

Predictor	Numerate (n or mean)	Not Numerate (n or mean)	p-value	Odds Ratio	95% CI for OR	p-value
Demographics						
Age	36.2[†]	33.3[†]	0.30	1.02	0.98-1.06	0.47
White race	22	41	--	--	--	--
Hispanic Ethnicity	0	5	--	--	--	--
Hemophilia Measures						
Hemophilia A	21	68	1.00[‡]	1.13	0.22 – 5.9	0.89
Severe Disease	16	60	0.29	0.60	0.21 – 1.73	0.34
Prophylaxis Regimen	10	38	0.55	0.81	0.31 – 2.12	0.67
Length of Time at HTC (years)	11.8[†]	17.0[†]	0.03	0.95	0.91-1.00	0.06
Any target joints	22	66	--	--	--	--
Other Health Measures						
HIV Positive	8	16	0.22	1.9	0.67 – 5.3	0.23
HCV Positive	14	40	0.64	1.27	0.47 – 3.4	0.64
On chronic medication(s)	14	27	0.04	2.72	1.01 – 7.4	0.05
Depression History	6	13	0.40	1.62	0.53 – 4.9	0.40
Socioeconomic Measures						
Annual Income ≥ $50,000	13	23	0.03	2.89	1.08-7.75	0.04
Completed undergrad or higher	14	19	<0.01	4.61	1.67-12.73	<0.01
Unemployed/Disabled	7	25	0.71	0.82	0.30-2.30	0.71
Owns car	20	51	0.14[‡]	3.53	0.75-16.6	0.11
Psychosocial Measures						
WFPTS Score	40.6[†]	43.3[†]	0.10	0.94	0.88-1.01	0.10
GSE Score	34.2[†]	34.3[†]	0.90	0.99	0.89-1.11	0.89
Haem-A-QoL Score	87.2[†]	100.5[†]	0.06	0.99	0.97-1.00	0.11

PCS	48.2†	44.1†	0.14	1.03	0.99-1.08	0.16
MCS	53.0†	55.0†	0.35	0.97	0.92-1.03	0.35

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†: The means of the continuous variables are listed.

‡: Used Fisher's Exact Test

HTC: Hemophilia Treatment Center; HIV: Human Immunodeficiency Virus; HCV: Hepatitis C Virus; WFPTS: Wake Forest Physician Trust Scale; GSE: General Self-Efficacy; PCS: Physical Component Score of SF-12; MCS: Mental Component Score of SF-12.

Table 5: Multivariable Linear Regression of the Association of Adherence with Health Literacy and Numerate status (n=91)†

Predictor	Beta Coefficient	Standard Error	p-value
s-TOFHLA score (per 10 points)	-0.90	2.17	0.67
Numerate (ref: SW score 0-2)	0.42	2.93	0.89

†The predictors are adjusted for the following confounders: length of time seen at the hemophilia treatment center, the Wake Forest Physician Trust Score, Haem-A-QoL, and education.

s-TOFHLA: shortened test of functional health literacy in adults. The higher the score, the better the health literacy

Table 6: Multivariable Linear Regression of the Association of Adherence with Predictor Measures (n=91) †

Predictor	Beta Coefficient	Standard Error	p-value
Depression history (ref: none)	7.13	2.80	0.01
On chronic medication(s) (ref: none)	-6.03	2.25	<0.01
Time seen at HTC (per 10 years)	-3.00	1.00	<0.01
WFPTS score (per 10 points)	-4.60	1.60	<0.01
Haem-A-QoL score (per 10 points)	1.30	0.30	<0.01

† Adjusted model for treatment type

HTC: Hemophilia Treatment Center; WFPTS: Wake Forest Physician Trust Score. The higher the score, the higher the physician trust; Haem-A-QoL: The lower the score, the better the quality of life

Figure 1: Simple Plot of Adherence and Health Literacy Score (n=91)

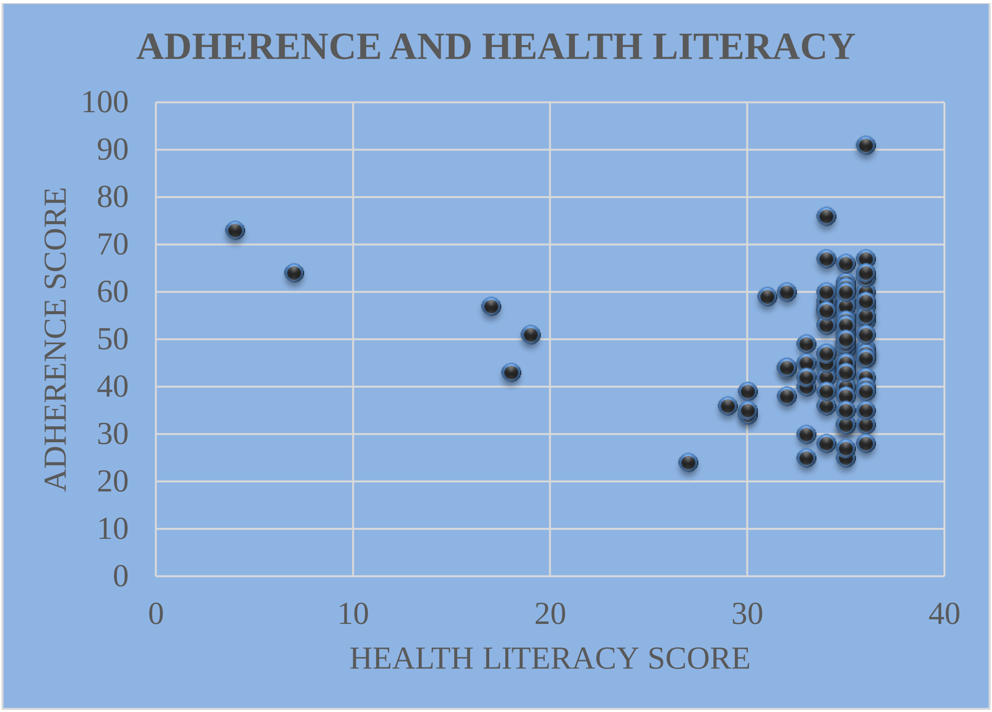

Figure 2: Simple Plot of Adherence and Numeracy Score (n=91)