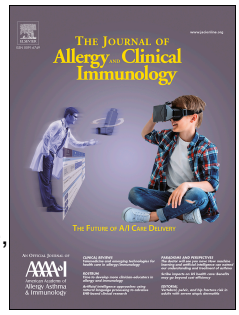
Journal Pre-proof



Prevalence of mastocytosis and hymenoptera venom allergy in the United States

Charles F. Schuler, IV, MD, Sofija Volertas, MD, Dilawar Khokhar, MD, Huseyin Yuce, PhD, Lu Chen, MS, MPH, Onur Baser, PhD, Jenny M. Montejo, MD, Cem Akin, MD

PII: S0091-6749(21)00652-7

DOI: https://doi.org/10.1016/j.jaci.2021.04.013

Reference: YMAI 15082

To appear in: *Journal of Allergy and Clinical Immunology*

Received Date: 11 January 2021

Revised Date: 26 March 2021

Accepted Date: 7 April 2021

Please cite this article as: Schuler IV CF, Volertas S, Khokhar D, Yuce H, Chen L, Baser O, Montejo JM, Akin C, Prevalence of mastocytosis and hymenoptera venom allergy in the United States, *Journal of Allergy and Clinical Immunology* (2021), doi: https://doi.org/10.1016/j.jaci.2021.04.013.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2021 Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology.

Journal Pre-proof

Prevalence of mastocytosis and hymenoptera venom allergy in the United States

Charles F. Schuler IV, MD*[1,2], Sofija Volertas, MD*[3], Dilawar Khokhar, MD[1], Huseyin Yuce, PhD[4], Lu Chen, MS, MPH[5], Onur Baser, PhD[6], Jenny M. Montejo, MD[7], Cem Akin, MD[1]

[1] Division of Allergy and Clinical Immunology, Department of Internal Medicine, University of Michigan, Ann Arbor, MI

[2] Mary H. Weiser Food Allergy Center, University of Michigan, Ann Arbor, MI

[3] Division of Rheumatology, Allergy and Immunology, Department of Internal Medicine, University of North Carolina, Chapel Hill, NC

[4] New York City College of Technology, New York, NY

[5] Columbia Data Analytics, LLC, New York, NY

[6] MEF University, Istanbul, Turkey

[7]Mayo Clinic, Rochester, MN

*Both authors contributed equally to this work.

Corresponding Author:

Charles Schuler

Address: Domino's Farms, 24 Frank Lloyd Wright Drive, Suite H-2100, Ann Arbor, MI 48106-0442, USA

Email: schulerc@med.umich.edu

Phone: 734-232-2154

Fax: 734-647-6263

Journal Pre-proof

Journal Pre-proof

Clinical Implications

Mastocytosis is less common among hymenoptera venom allergy patients in the United States than in Europe. Basal serum tryptase elevations may predict venom immunotherapy reactions.

Capsule Summary

Mastocytosis is less common in hymenoptera venom allergy patients in the United States versus Europe. However, elevated basal serum tryptase may predict venom immunotherapy reactions, supporting the recommendation to check this in venom anaphylaxis patients.

Key words

Tryptase, venom allergy, venom immunotherapy, anaphylaxis, mastocytosis, mast cell activation syndrome, mast cell disease

Abbreviations

Hymenoptera venom allergy (HVA)

United States (US)

Venom immunotherapy (VIT)

Mast Cell Disease (MCD)

American Academy of Allergy, Asthma, and Immunology (AAAAI)

Journal Pre-proof

Journal Pre-proof

Word Count: 3506

Funding and Conflict of Interest

This work described herein was not directly supported by any funding body. Dr. Schuler reports salary and other support from the Mary H. Weiser Food Allergy Center and the Taubman Innovation Institute at UM; he has also received sponsored project support from Healgen Scientific and Access Bio Inc for unrelated projects. The other authors report no conflicts of interest.

Journal Pre-proof

Journal Pre-proof

Abstract

Background: Mastocytosis is a risk factor for hymenoptera venom anaphylaxis (HVA). Current guidelines recommend measuring tryptase in HVA patients and that those with mastocytosis pursue lifelong venom immunotherapy (VIT). Available data on HVA and mastocytosis largely derives from European single-center studies and the prevalence of HVA with and without mastocytosis in the United States (US) is unknown.

Objective: We sought to determine the prevalence of HVA and mastocytosis in the US using an insurance claims database and evaluate the impact of mastocytosis on VIT in HVA patients in a US cohort.

Methods: The IBM Watson Database, consisting of insurance claims from approximately 27 million US patients in 2018, was queried to identify patients with HVA and/or mastocytosis. Further, a retrospective study of 161 patients undergoing VIT between 2015 – 2018 at the University of Michigan (U-M) was conducted.

Results: In the IBM Watson Database, the prevalence of HVA was 167 per 100,000 (0.167%) and the prevalence of mastocytosis 10 per 100,000 (0.010%) overall and 97 per 100,000 (0.097%) among those with HVA. Mastocytosis showed a 9.7-fold increase among HVA patients versus the general population. In the U-M cohort, 2.6% of VIT patients had mastocytosis. Tryptase level did not correlate with venom reaction severity but was higher in patients with systemic VIT reactions.

Conclusions: We observed a lower US HVA prevalence than previously reported. Mastocytosis was more common in US HVA patients, though at lower rates than previously reported. In VIT patients there was no correlation between tryptase level and reaction severity.

Journal Pre-proof

Journal Pre-proof

Introduction

Hymenoptera venom allergy (HVA) constitutes an IgE-mediated anaphylactic reaction with a prevalence from 0.5% to 3.3% in the United States (US) and 0.3% to 7.5% in Europe (1, 2). Patients are prescribed epinephrine as a rescue medicine and may undergo prophylactic venom immunotherapy (VIT); VIT for honeybee, vespids, and wasp reduces systemic reaction rates from 60% in untreated patients to as low as 0-5% (3-5). VIT is recommended for patients with anaphylactic venom reactions (3, 5).

Prior work has shown a high prevalence among HVA patients of up to 11.6% (or 11,600 per 100,000) with elevated serum tryptase and up to 5.5% (or 5,500 per 100,000) for clonal mast cell (MC) disease (MCD), including systemic mastocytosis (SM) (6, 7). Elevated serum tryptase has been linked to severe sting reactions and reactions during VIT (8, 9). The diagnosis of SM also marks an increased risk for severe sting reactions and adverse events during VIT (10, 11). Thus, updated AAAAI guidelines for HVA patients have expanded recommendations for tryptase measurement in this population (3). However, much of the work supporting high rates of SM in HVA patients comes from European single-center studies many of which were also referral centers for mastocytosis and may have carried a selection bias. In addition, these studies were also performed prior to recognition of hereditary alpha tryptasemia (6, 7, 12). A recent single-center study of 159 patients from Israel found a lower rate of tryptase elevation and MC disease when compared to European data (3.8% as compared to 10-15.9%), suggesting geographic differences in co-occurrence of MCD and venom allergy may exist. (13). The rate of clonal MCD in the US HVA population remains unknown.

Journal Pre-proof

Journal Pre-proof

We hypothesized that among HVA and VIT patients, the rate of MCD and elevated tryptase levels would be lower than European data. We further sought to evaluate the role of tryptase as a predictive marker in VIT patients given updated guidelines.

Journal Pre-proof

Journal Pre-proof

Methods

Database

The IBM Watson MarketScan® Research Database was queried for patients with a diagnosis of HVA (ICD-10 codes T63.44, T63.45, T63.46, Z91.030, Z91.038) and Mastocytosis (ICD-10 codes D47.01, D47.02, D47.09, C96.21, C94.3). This database consists of de-identified outpatient, inpatient, and pharmaceutical claims of approximately 27 million privately insured patients in 2018. Complete claims originate from over 150 large employer-sponsored health insurance plans with patient coverage in all 50 states. Real world data from January 1st, 2018 through December 31st, 2018 was obtained for analysis. Eligible patients had 6-12 months of claims data in 2018.

Allergy Clinic Patient Population

We conducted a retrospective study of 161 patients with a history of systemic venom reactions and received venom immunotherapy injections between 2015 and 2018 at the University of Michigan Allergy and Immunology clinic. The University of Michigan Medical School Institutional Review Board on Human Subjects (IRB) reviewed and cleared the protocol. Written informed consent was not required because of the retrospective nature of the study.

Venom Immunotherapy Protocol

Patients were selected by the treating physician to undergo VIT based on available practice parameter guidelines. A history of a venomous sting followed by an allergic reaction, including a combination of diffuse urticaria, angioedema,

Journal Pre-proof

Journal Pre-proof

gastrointestinal distress (including nausea, vomiting, or diarrhea), respiratory symptoms (including cough, wheeze, or dyspnea), loss of consciousness, or documented low blood pressure was needed to begin venom immunotherapy (3, 5). Patients diagnosed prior to the 2017 US guidelines may have started VIT based on a systemic cutaneous reaction according to earlier guidelines and were not excluded from this study (14). Positive skin or blood specific IgE testing to honeybee, yellow jacket, yellow hornet, white-faced hornet, or wasp was required. Positive skin testing was defined as a wheal of 3 mm greater than the negative control on skin prick or intradermal testing; we note the guideline statements of uncertainty on the intradermal test cutoff, 3 mm over the negative control was used in this study as it is the consensus among the U-M allergy group where the study took place (3). Positive blood testing was defined as any serum IgE level to a venom above the normal range (< 0.35 kU/L) (3). Patients were counseled on risks and benefits by the treating physician in the course of standard clinical care.

Venom immunotherapy at the University of Michigan follows US guidelines (3). A monthly maintenance dose of 1 mL of 100 mcg/mL concentrate for each venom, or 1 mL of 300 mcg/mL for mixed vespid (yellow jacket, yellow hornet, and white-faced hornet), is used. 0.05 mL of dilutions down to 1:1000 of concentrate, or lower, are used to build up weekly to maintenance.

Mastocytosis was diagnosed by the treating physician and the diagnosis was verified by the study team after reviewing the bone marrow biopsy report and tryptase values. Mastocytosis was defined according to the 2016 WHO diagnosis and classification system (15).

Journal Pre-proof

Data Collection

A standardized approach was used to collect pre-specified variables from patients' charts. Demographic data included age, gender, and race/ethnicity. Medical history included a history of asthma, atopic sensitization, food allergy, atopic dermatitis, family history of systemic venom allergy reactions, coronary artery disease, ACE inhibitor use, and beta blocker use. A positive skin test (a wheal of 3 mm greater than the negative control) to at least one allergen defined atopy (16). Allergens tested included trees, grasses, weeds, molds, dust mite, cat, and dog. The original venom reaction was coded according to the presence or absence of hives/rash, angioedema, respiratory symptoms (cough, dyspnea, or wheezing), gastrointestinal symptoms (nausea, vomiting, diarrhea), flushing, loss of consciousness, and low blood pressure. All reactions were graded I – IV based on a modified Mueller anaphylaxis scale (17).

Venom skin testing was recorded. For both skin prick and intradermal testing, wheal and flare in millimeters were recorded. For blood testing, total IgE and individual venom IgE levels were recorded. Sensitivity to a venom was recorded as a positive skin or blood test.

Venom immunotherapy characteristics was recorded, including the time to maintenance, time on maintenance, total reactions, large local reactions and systemic reactions (diagnosed by the treating physician).

Subsequent venom reactions in the field after starting VIT were recorded identically as the original venom reaction. Tryptase laboratory order status, draw status, date, and the value were recorded. If a bone marrow biopsy occurred, the pathologic

Journal Pre-proof

Journal Pre-proof

presence of mast cell disease (MCD), subtype, and number of major and minor criteria for mastocytosis were recorded (18, 19).

Statistical Analysis

IBM SPSS version 22 (Armonk, NY) statistical software and GraphPad Prism (San Diego, CA) were used to perform all statistical analysis. Potentially significant ($p < 0.2$) associations between patient characteristics and data of interest were initially evaluated via bivariate correlation and chi-squared analysis. Linear or logistic regression analysis was then performed as appropriate on all potentially significant variables to create multivariate associations. A Cochran-Mantel-Haenszel (CMH) test was used to compare prevalence of mastocytosis in patients with HVA compared to those with mastocytosis without HVA in the database; this was stratified by adult vs pediatric patients.

Journal Pre-proof

Journal Pre-proof

Results

Database results

The database query included 27,299,530 distinct patients in calendar year 2018. This revealed a prevalence of 166.8 per 100,000 for HVA overall. Mastocytosis prevalence was 10.1 per 100,000 overall and 96.7 per 100,000 (or 0.0967%) amongst HVA patients in 2018; an odds ratio of 9.7 (95% CI 7.2 – 13.1, p <0.0001) was noted when comparing mastocytosis in patients with HVA compared to those without in 2018 (Figure 1). Among adult (age 18 years and older) patients, the odds ratio was 14.3 (95% CI 10.5 – 19.6, p < 0.0001). Among pediatric (age < 18 years) patients, there was no statistical significance (odds ratio 2.4 (95% CI 0.9 – 6.4, p = 0.07).

Patient Characteristics

Given the increased prevalence of mastocytosis in real world data, we investigated the data from our allergy practice in patients with systemic reactions to hymenoptera, undergoing VIT. University of Michigan is a referral center for MCD. Table 1 displays the demographic and disease-specific characteristics for the patients in the University of Michigan cohort. The mean age was 47.6 and ranged from 7 – 81 years old. 41% were female. 24% carried a diagnosis of asthma, 41% had a history of atopic sensitization to a non-venom allergen. 8% had a family history of venom allergy.

The average Mueller anaphylaxis grade for the patients' original reactions was 2.90. This included 34% of patients with a documented low blood pressure and 26% of patients who lost consciousness. Further, 66% experienced hives or rash, 61% angioedema, 48% respiratory symptoms, and 12% gastrointestinal symptoms. 71% of

patients were sensitized to honeybee, 85% to yellow jacket, 68% to yellow hornet, 73% to white-faced hornet, and 68% to wasp. During venom immunotherapy, 10% experienced a systemic reaction.

Impact of VIT on venom allergy course

VIT was effective in this venom allergy population. Among these 161 patients who began immunotherapy, 26 (16%) suffered a subsequent venom reaction (table 1). The mean Mueller grade of these subsequent reactions was 0.96 (table 1), significantly lower than the mean grade of initial reactions (Fig. 2A). This shows that venom reactions after VIT were less frequent and less severe than before VIT started.

We sought to find variables associated with a subsequent venom reaction after VIT initiation. Using logistic regression, the only significantly correlated variable was a family history of a systemic venom reaction, with an odds ratio of 8.8 ($p = 0.049$) (table 2). 4% of patients who did not have subsequent venom reactions had a family history of a systemic venom reaction, significantly fewer than the 25% rate in patients who did have a subsequent venom reaction (Fig. 2B).

Impact of guideline update on practice

American practice guidelines published in January 2017 recommend measuring tryptase levels for patients with cardiovascular compromise with venom reactions; these guidelines suggest consideration of tryptase measurement for all patients with evidence of venom anaphylaxis (3). We sought to evaluate the impact of these guidelines on clinical practice in an academic allergy center. Among patients who did not lose

Journal Pre-proof

consciousness during the initial venom reaction, the rate of tryptase measurement was 52%, significantly lower than the 81% among patients who lost consciousness during the initial reaction (Fig. 3A). Before 2017, the rate of tryptase measurement in VIT patients was 59%; after 2017, the rate was 100%, significantly higher (Fig. 3B).

Elevated tryptase and clonal MCD in VIT population

We found 9 patients (5.6%) to have a baseline tryptase level greater than >11.5 ng/mL. Among these, 4 patients underwent bone marrow biopsy and 3 (1.8% of total) had clonal MCD. Two of these had indolent SM and 1 had monoclonal mast cell activation syndrome. These patients had significantly higher tryptase levels than patients who had a tryptase measured but no known MCD (Fig. 4A).

We sought to evaluate whether tryptase levels correlates with other key features of HVA. Among patients who had a tryptase level, tryptase did not correlate with the initial reaction Mueller anaphylaxis grade (Fig. 4B). Elevated tryptase levels appeared in patients throughout the grading scale. We also sought whether tryptase or other variables might correlate with a low blood pressure, an indicator of cardiovascular compromise, during the initial reaction. On logistic regression the only significantly correlated variables were loss of consciousness, with an odds ratio of 12.9 ($p < 0.0001$), and having a tryptase drawn, with an OR of 2.6 ($p = 0.039$) (table 2). Tryptase level, whether analyzed as a continuous variable or when broken into discrete groups of 0 – 5 ng/mL, 5 – 11.4 ng/mL, and over 11.4 ng/mL, did not correlate with low blood pressure during the initial reaction. However, tryptase levels divided according to the same levels did correlate with loss of consciousness (LOC). Patients with tryptase levels between 5

Journal Pre-proof

Journal Pre-proof

– 11.4 ng/mL had the highest rate of LOC at 50%, significantly higher than the rate of 11% in those with a tryptase greater than 11.4 ng/mL (Fig. 4C).

Because systemic reactions during VIT are a key adverse effect and worse reactions have been correlated with higher tryptase levels previously (9), we evaluated whether this was true in our population. We found a significantly higher mean tryptase level among patients who had a systemic VIT reaction versus patients who did not (Fig. 4D). Furthermore, to find variables correlated with having a systemic VIT reaction, we used a multivariate logistic regression that involved all bivariate associations where p was less than 0.2; the only significantly correlated variable was tryptase level, with an odds ratio of 1.3 ($p = 0.027$) per unit increase in tryptase level (table 2). Notably, beta blocker and ACE-inhibitor use did not correlate with the presence, number, or severity of a systemic VIT reaction.

Journal Pre-proof

Journal Pre-proof

Discussion

VIT is an effective preventative therapy for HVA (3, 5). US guidelines recommend considering a baseline tryptase level for all HVA patients undergoing VIT and outright recommend to check in severe venom anaphylaxis (3). Given a high rate of MCD amongst patients with HVA, up to 7-11%, some authors suggest measuring tryptase values in all VIT patients (6, 7, 20). SM is associated with failure of VIT, prompting the noted increased vigilance (10). Bonadonna et al found that among HVA patients, 11.6% had tryptase levels >11.4 and clonal MCD was detected in 90.9% of patients with elevated tryptase who underwent further evaluation; at a minimum, 5.5% of the total (a rate of 5,500 per 100,000) were diagnosed with systemic mastocytosis (7). Further, one study suggests that patients with severe hypotension and normal basal tryptase values have rates of MCD up to 75% (21). However, a recent publication from Israel demonstrated a MCD rate of 3.8% (or 3,800 per 100,000) amongst HVA patients (13), lower than the figures cited in European data. The rate, to our knowledge, has not been reported in a US population. In this work, we report a MCD rate among HVA patients of 0.097% in the US population. While this rate cannot be statistically compared directly to the European or Israeli reports (7, 13) because the current estimate encompasses a data set of millions versus prior reports involving hundreds patients, this reported rate is qualitatively lower than prior reports by over an order of magnitude. One explanation for the higher previously reported rate could be that prior studies occurred mainly within referral centers for mastocytosis and may have carried a selection bias.

Prior work suggests 56-94% of adults report at least one lifetime hymenoptera sting (22), and the rate of systemic reactions among those who are stung is 0.5-3.3% in

the United States (23) and 0.3-7.5% in Europe (5). We report a one-year prevalence of 0.167% in 2018 in a US cohort, lower than prior reports. Another explanation could be that our data includes subjects with 6-12 months of data, which might lower the rate of HVA detected here, as some patients may not have had claims data during this period. This is a limitation shared with other claims database-based analyses. Furthermore, the database used in this study does not necessarily include non-privately insured patients, so the population may not fully represent the entire United States population, thereby affecting prevalence. The rate of systemic reactions to insects in the US and Europe are similar, suggesting similar rates of hymenoptera allergy; this could change with variances in insect species' distribution. For example, climate change may promote habitats favorable to invasive insects (24); as the number of insect stings changes by region the incidence of HVA may also change as recurrent stings have been described as a risk factor for HVA (23). Another factor that may affect the rate of MCD within the HVA population is the total MCD burden by population; the prevalence of mastocytosis in the general population is estimated to be 3 to 13 per 100,000 inhabitants (25). Our finding of 7.7 per 100,000 falls within the previously reported range. Thus, there might be a disproportionate change in the incidence of HVA relative to the incidence of mast related diseases.

Another consideration is the etiology of an elevated tryptase. It has been estimated that 4-6% of the population has an elevated tryptase (12). Most of these patients do not have a clonal MCD. Hereditary alpha-tryptasemia (HAT) is a recently described autosomal dominant trait caused by increased monoallelic α-tryptase copy number at *TPSAB1* (12). Much of the prior work examining elevated serum tryptase in

Journal Pre-proof

HVA patients was performed before the recognition of HAT as a distinct entity, which may have impacted mast cell disease estimates at that time. It has only been recently that role of HAT in HVA has been examined. Cohort studies have suggested HAT is associated with more severe HVA, but may not affect the rate of HVA as the rate of HAT in some HVA patient cohorts is similar to that of the general population (26, 27). HAT may be overrepresented in patients with clonal MCD and these may have a synergistic effect on severity of anaphylaxis (26, 27). If HAT does affect anaphylaxis severity this may explain why some patients with MCDs have more severe HVA versus others and why elevated serum tryptase without clonal MCD has been at times associated with HVA severity. The role of HAT in HVA is an area that requires further investigation.

Race is increasingly recognized as a factor in many atopic diseases (28). It has been implicated in not only outcomes disparities, but also in the immunology and genetics of atopy. The US has a racially and ethnically diverse population. This heterogeneity of this group could explain differences in MCD and HVA in the US population compared to Europe. Role of ethnic background in mast cell related disease and HVA are two areas that require further investigation.

The lower rate of MCD in this study may be due to various factors. The IBM database relies on the proper coding of the diagnoses of hymenoptera allergy and mastocytosis. The accuracy of coding can vary with literature suggesting rates of error from 0-70% (29). This suggests that a significant number of HVA patients are not screened for MCD. Another limitation is the method diagnosis for HVA, as the initial reaction and allergy testing is not reported. Because up to 25% of adults may have

Journal Pre-proof

hymenoptera sensitization (30), it is possible that patients with non-anaphylactic insect sting reactions and sensitization to hymenoptera were mislabeled as HVA.

The role of baseline tryptase in the course of VIT has been explored. Higher basal tryptase levels have been proposed to predict a high risk of VIT side effects, particularly during build-up (9). Elevated basal tryptase has also been associated with severe sting reactions (8, 31, 32), including hypotension and fatality (33). In this work, the tryptase level was not correlated with the severity of the initial reaction, though this study involves only those on VIT, which may be a confounding factor. In fact, patients with the tryptase levels over 11.4 ng/mL had less frequent loss of consciousness than those with lower tryptase levels (Fig 4C). We do note that in patients with known mastocytosis, patients with higher basal serum tryptase (e.g. 40 ng/ml or above) are less likely to have anaphylaxis than those with mild to moderate elevations (34), so perhaps a similar effect is occurring here in this broader population; more work would be needed to address this further (11). As our cohort specifically examined VIT patients, we cannot assess whether tryptase levels correlate with severity of initial reactions among patients with anaphylactic reactions versus patients with non-anaphylactic reactions (as that group does not typically undergo VIT). An elevated baseline tryptase was associated here with systemic reactions to VIT, consistent with prior published work.

Allergists may have increased suspicion of underlying mastocytosis when particular characteristics of the sting reaction are present, such as hypotension without hives, especially in males (35). This was reflected in our data, as the treating allergist was more likely to draw a tryptase level in patients who presented with a low blood

Journal Pre-proof

pressure (Fig. 3A). Furthermore, the guideline changes in the US in 2017 (3) appeared to impact practice patterns, as all VIT patients started after 2017 had a tryptase level drawn, compared with before 2017 (Fig. 3B).

Prior authors have suggested no association between anaphylaxis severity and comorbidities or cardiovascular medications (20, 36). Our data were supportive of this as well; beta blocker use, ACE-inhibitor use, and cardiovascular disease were not associated with initial reaction severity, subsequent reaction rate or severity, nor with the rate of systemic reactions while patients were on VIT.

Prior literature has suggested an association between HVA and MCD based on several observations. The prevalence of HVA in SM is higher than the general population and HVA represents the most common anaphylaxis trigger in adult mastocytosis patients; there is also more frequent clonal MCD in patients with systemic HVA than the general population (37). This study supports a relationship between HVA and mastocytosis with the prevalence of mastocytosis among patients with HVA being 12 fold higher than among the general population.

In conclusion, mastocytosis may be less common in the US population compared to European reports with systemic venom reactions, but a strong association remains between HVA and mastocytosis. In this population of VIT patients, serum tryptase values do not correlate with severity of venom reactions; indeed, higher levels may correlate with less frequent loss of consciousness. Baseline serum tryptase elevation does correlate with more frequent systemic VIT reactions. Beta blocker and ACE-inhibitor use in this population do not correlate with the frequency or severity of venom or VIT reactions. Overall, these data suggest that while baseline serum tryptase may

Journal Pre-proof

Journal Pre-proof

help identify MCD patients amongst the HVA population and help predict systemic reactions to VIT, the MCD rate may be lower in this US population than other populations.

Journal Pre-proof

Journal Pre-proof

Acknowledgements

The authors acknowledge the patients who contributed data for this work and the University of Michigan Allergy Clinic staff who perform venom immunotherapy and clinical care with the excellence and consistency that allows this sort of work to proceed.

Journal Pre-proof

References

1. Bilo MB, Bonifazi F. The natural history and epidemiology of insect venom allergy: clinical implications. Clin Exp Allergy. 2009;39(10):1467-76.
2. Golden DB, Marsh DG, Kagey-Sobotka A, Freidhoff L, Szklo M, Valentine MD, et al. Epidemiology of insect venom sensitivity. JAMA. 1989;262(2):240-4.
3. Golden DB, Demain J, Freeman T, Graft D, Tankersley M, Tracy J, et al. Stinging insect hypersensitivity: A practice parameter update 2016. Ann Allergy Asthma Immunol. 2017;118(1):28-54.
4. Hunt KJ, Valentine MD, Sobotka AK, Benton AW, Amodio FJ, Lichtenstein LM. A controlled trial of immunotherapy in insect hypersensitivity. N Engl J Med. 1978;299(4):157-61.
5. Sturm GJ, Varga EM, Roberts G, Mosbech H, Bilo MB, Akdis CA, et al. EAACI guidelines on allergen immunotherapy: Hymenoptera venom allergy. Allergy. 2018;73(4):744-64.
6. Bonadonna P, Zanotti R, Pagani M, Caruso B, Perbellini O, Colarossi S, et al. How much specific is the association between hymenoptera venom allergy and mastocytosis? Allergy. 2009;64(9):1379-82.
7. Bonadonna P, Perbellini O, Passalacqua G, Caruso B, Colarossi S, Dal Fior D, et al. Clonal mast cell disorders in patients with systemic reactions to Hymenoptera stings and increased serum tryptase levels. J Allergy Clin Immunol. 2009;123(3):680-6.
8. Blum S, Gunzinger A, Muller UR, Helbling A. Influence of total and specific IgE, serum tryptase, and age on severity of allergic reactions to Hymenoptera stings. Allergy. 2011;66(2):222-8.
9. Rueff F, Przybilla B, Bilo MB, Muller U, Scheipl F, Aberer W, et al. Predictors of side effects during the buildup phase of venom immunotherapy for Hymenoptera venom allergy: the importance of baseline serum tryptase. J Allergy Clin Immunol. 2010;126(1):105-11 e5.
10. Gonzalez de Olano D, Alvarez-Twose I, Esteban-Lopez MI, Sanchez-Munoz L, de Durana MD, Vega A, et al. Safety and effectiveness of immunotherapy in patients with indolent systemic mastocytosis presenting with Hymenoptera venom anaphylaxis. J Allergy Clin Immunol. 2008;121(2):519-26.
11. van Anrooij B, van der Veer E, de Monchy JG, van der Heide S, Kluin-Nelemans JC, van Voorst Vader PC, et al. Higher mast cell load decreases the risk of Hymenoptera venom-induced anaphylaxis in patients with mastocytosis. J Allergy Clin Immunol. 2013;132(1):125-30.
12. Lyons JJ, Yu X, Hughes JD, Le QT, Jamil A, Bai Y, et al. Elevated basal serum tryptase identifies a multisystem disorder associated with increased TPSAB1 copy number. Nat Genet. 2016;48(12):1564-9.
13. Hershko AY, Shaharabani N, Rosman Y, Meir-Shafrir K, Lachover-Roth I, Cohen Engler A, et al. Hymenoptera venom allergy in a single-center Israeli cohort: Clinical and laboratory characteristics. J Allergy Clin Immunol Pract. 2019.
14. Golden DB, Moffitt J, Nicklas RA, Freeman T, Graft DF, Reisman RE, et al. Stinging insect hypersensitivity: a practice parameter update 2011. J Allergy Clin Immunol. 2011;127(4):852-4 e1-23.
15. Valent P, Akin C, Metcalfe DD. Mastocytosis: 2016 updated WHO classification and novel emerging treatment concepts. Blood. 2017;129(11):1420-7.
16. Bernstein IL, Li JT, Bernstein DI, Hamilton R, Spector SL, Tan R, et al. Allergy diagnostic testing: an updated practice parameter. Ann Allergy Asthma Immunol. 2008;100(3 Suppl 3):S1-148.
17. Mueller HL. Diagnosis and treatment of insect sensitivity. J Asthma Res. 1966;3(4):331-3.
18. Volertas S, Schuler CFt, Akin C. New Insights into Clonal Mast Cell Disorders Including Mastocytosis. Immunol Allergy Clin North Am. 2018;38(3):341-50.
19. Valent P, Akin C, Hartmann K, Nilsson G, Reiter A, Hermine O, et al. Advances in the Classification and Treatment of Mastocytosis: Current Status and Outlook toward the Future. Cancer Res. 2017;77(6):1261-70.

Journal Pre-proof

435 20. Stoevesandt J, Hain J, Kerstan A, Trautmann A. Over- and underestimated parameters in severe
436 Hymenoptera venom-induced anaphylaxis: cardiovascular medication and absence of
437 urticaria/angioedema. J Allergy Clin Immunol. 2012;130(3):698-704 e1.
438 21. Zanotti R, Lombardo C, Passalacqua G, Caimmi C, Bonifacio M, De Matteis G, et al. Clonal mast
439 cell disorders in patients with severe Hymenoptera venom allergy and normal serum tryptase levels. J
440 Allergy Clin Immunol. 2015;136(1):135-9.
441 22. Bilo BM, Bonifazi F. Epidemiology of insect-venom anaphylaxis. Curr Opin Allergy Clin Immunol.
442 2008;8(4):330-7.
443 23. Golden DB. Anaphylaxis to insect stings. Immunol Allergy Clin North Am. 2015;35(2):287-302.
444 24. Vega A, Castro L. Impact of climate change on insect-human interactions. Curr Opin Allergy Clin
445 Immunol. 2019;19(5):475-81.
446 25. Brockow K. Epidemiology, prognosis, and risk factors in mastocytosis. Immunol Allergy Clin
447 North Am. 2014;34(2):283-95.
448 26. Lyons JJ, Chovanec J, O'Connell MP, Liu Y, Selb J, Zanotti R, et al. Heritable risk for severe
449 anaphylaxis associated with increased alpha-tryptase-encoding germline copy number at TPSAB1. J
450 Allergy Clin Immunol. 2020.
451 27. O'Connell MP, Lyons JJ. Hymenoptera venom-induced anaphylaxis and hereditary alpha-
452 tryptasemia. Curr Opin Allergy Clin Immunol. 2020;20(5):431-7.
453 28. Castells M. Race and allergy: Are we that different? Ann Allergy Asthma Immunol.
454 2019;122(5):439-40.
455 29. O'Malley KJ, Cook KF, Price MD, Wildes KR, Hurdle JF, Ashton CM. Measuring diagnoses: ICD
456 code accuracy. Health Serv Res. 2005;40(5 Pt 2):1620-39.
457 30. Abrams EM, Golden DBK. Approach to Patients with Stinging Insect Allergy. Med Clin North Am.
458 2020;104(1):129-43.
459 31. Rueff F, Przybilla B, Bilo MB, Muller U, Scheipl F, Aberer W, et al. Predictors of severe systemic
460 anaphylactic reactions in patients with Hymenoptera venom allergy: importance of baseline serum
461 tryptase-a study of the European Academy of Allergology and Clinical Immunology Interest Group on
462 Insect Venom Hypersensitivity. J Allergy Clin Immunol. 2009;124(5):1047-54.
463 32. Ludolph-Hauser D, Rueff F, Fries C, Schopf P, Przybilla B. Constitutively raised serum
464 concentrations of mast-cell tryptase and severe anaphylactic reactions to Hymenoptera stings. Lancet.
465 2001;357(9253):361-2.
466 33. Haeberli G, Bronnimann M, Hunziker T, Muller U. Elevated basal serum tryptase and
467 hymenoptera venom allergy: relation to severity of sting reactions and to safety and efficacy of venom
468 immunotherapy. Clin Exp Allergy. 2003;33(9):1216-20.
469 34. Gulen T, Ljung C, Nilsson G, Akin C. Risk Factor Analysis of Anaphylactic Reactions in Patients
470 With Systemic Mastocytosis. J Allergy Clin Immunol Pract. 2017;5(5):1248-55.
471 35. Golden DBK, Carter MC. Insect Sting Anaphylaxis-Or Mastocytosis-Or Something Else? J Allergy
472 Clin Immunol Pract. 2019;7(4):1117-23.
473 36. Smith MA, Newton LP, Barcena Blanch MA, Cuervo-Pardo L, Cho L, Newton D, et al. Risk for
474 Anaphylactic Reaction From Cardiac Catheterization in Patients Receiving beta-Adrenergic Blockers or
475 Angiotensin-Converting Enzyme-Inhibitors. J Allergy Clin Immunol Pract. 2019.
476 37. Bonadonna P, Scaffidi L, Boni E. Tryptase values in anaphylaxis and insect allergy. Curr Opin
477 Allergy Clin Immunol. 2019;19(5):462-7.

478

479

Journal Pre-proof

Figure Legends

Figure 1: In 2018, the prevalence of Mastocytosis among patients with hymenoptera allergy was 9.7 times more than the prevalence among the US general population. Note: OR = odds ratio, 95% confidence interval listed in parentheses.

Figure 2: A) Mueller grade of initial reaction (mean 2.90, n=158) compared to Mueller grade of any subsequent reactions (mean 0.96, n=23). B) The proportion of patients with a family history of a systemic venom reaction is stratified according to whether the patient did (4%, n=126) or did not (25%, n=25) have a subsequent venom reaction after a VIT course. Data represent mean +/- standard error of the mean (SEM). *** $p < 0.001$, **** $p < 0.0001$.

Figure 3: A) Rate of tryptase measurement stratified by blood pressure drop presence (52%, n=104) or absence (81%, n=54) at initial reaction. B) Rate of tryptase measurement rate stratified by date, before 2017 (59%, n=150) or after the start of 2017 (100%, n=11). Data represent mean +/- standard error of the mean (SEM). ** $p < 0.01$, *** $p < 0.001$.

Figure 4: A) Tryptase level stratified by whether a MCD was present (mean 18.0, n = 3) or not present (mean 5.0, n = 93). B) Tryptase levels are plotted according to the Mueller grade of the patient's initial venom reaction. Mean tryptase: Grade 1 = 7.0 (n=4), Grade 2 = 6.0 (n=15), Grade 3 = 5.2 (n=41), Grade 4 = 5.1 (n=34). C) The proportion of patients with loss of consciousness (LOC) is plotted based on the tryptase

Journal Pre-proof

Journal Pre-proof

level, with ranges of < 5 ng/mL (34%, n=62), 5 – 11.4 ng/mL (50%, n=24), and > 11.4 ng/mL (11%, n=9). D) Tryptase levels are plotted for patients who did (mean 8.8, n=7) or did not (mean 5.1, n=73) have systemic reactions during venom immunotherapy (VIT). Data represent mean +/- SEM. *p < 0.05, **p < 0.01, ****p < 0.0001.

Tables

Patient characteristic	**All patients (n=161)**	**Adults (n=147)**	**Children (n=14)**
Demographic			
Age (mean years [range])	47.6 (7-81)	50.8 (18-81)	13.2 (7-17)
Gender (n [% female])	66 (41)	65 (44)	1 (7)
General disease history			
History of asthma (n [%])	39 (24)	35 (24)	4 (29)
History of other atopic sensitization (n [%])	66 (41)	63 (43)	3 (21)
History of atopic dermatitis (n [%])	15 (9)	10 (7)	5 (36)
History of food allergy (n [%])	8 (5)	7 (5)	1 (7)
Family history of venom allergy (n [%])	13 (8)	9 (6)	4 (29)
Beta blocker use (n [%])	7 (4)	7 (5)	0 (0)
ACE inhibitor use (n [%])	9 (6)	9 (6)	0 (0)
Original venom reaction			
Hives or rash (n [%])	106 (66)	96 (65)	10 (71)
Angioedema (n [%])	99 (61)	88 (60)	11 (79)
Respiratory symptoms (n [%])	78 (48)	71(48)	8 (57)
Gastrointestinal symptoms (n [%])	19 (12)	15 (10)	4 (29)
Low blood pressure documented (n [%])	54 (34)	53 (36)	1 (7)
Loss of consciousness (n [%])	42 (26)	41 (28)	1 (7)
Mueller anaphylaxis grade (mean [SD])	2.90 (0.88)	2.92 (0.90)	2.71 (0.61)
Venom sensitization			
Honeybee (n [%])	115 (71)	107 (73)	8 (57)
Yellow jacket (n [%])	137 (85)	127 (86)	10 (71)
Yellow hornet (n [%])	110 (68)	101 (69)	9 (64)
White-faced hornet (n [%])	117 (73)	107 (73)	10 (71)
Wasp (n [%])	110 (68)	101 (69)	9 (64)
Venom IT course			
Systemic reaction to IT (n [%])	16 (10)	15 (10)	1 (7)
Subsequent venom reaction (n [%])	24 (15)	18 (12)	6 (43)
Subsequent venom reaction Mueller grade (mean [SD])	0.96 (0.98)	1.13 (0.97)	0.57 (0.98)
Tryptase measurement			

Journal Pre-proof

Tryptase drawn (n [%])	99 (61)	91 (62)	8 (57)
Tryptase value (mean ng/mL [range])	5.4 (1.5 - 20.9)	5.5 (1.5 - 20.9)	4.4 (2.3 - 8.4)
MCD (% all patients [% if tryptase measured])	1.9 (2.6)	2.0 (3.2)	0 (0)

Table 1: The baseline characteristics of the patient population are listed in aggregate and by adults (age 18 and up) and children (age < 18). SD = standard deviation. Mueller grading delineated in Methods section (17).

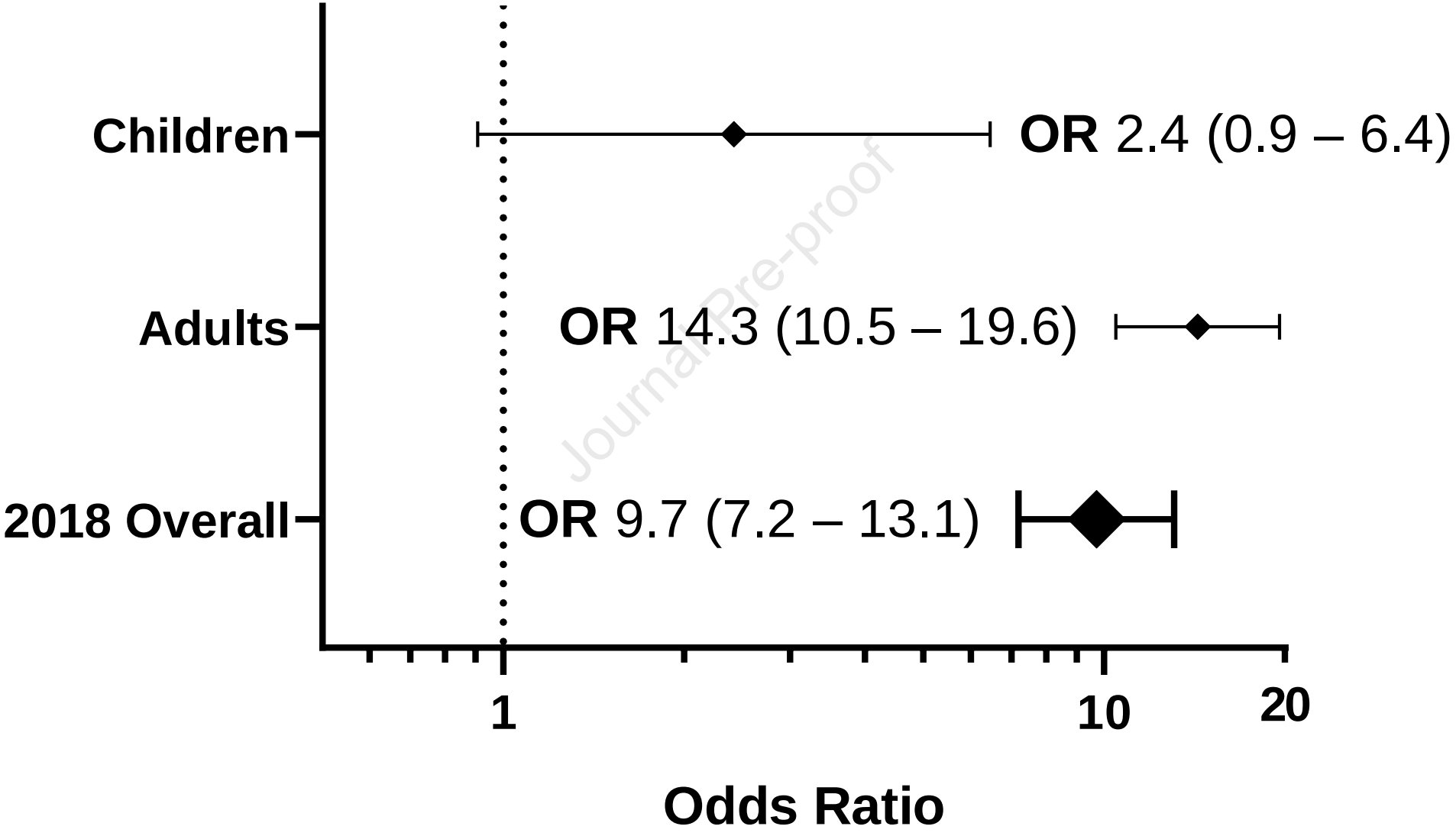
Dependent variable	**Independent variables**	**Odds Ratio**	**p - value**
Systemic IT reaction	Tryptase	1.3	0.027
Low blood pressure on first reaction	LOC on first reaction	12.9	<0.001
	Tryptase drawn	2.6	0.039
Subsequent venom reaction	Family history of systemic venom reaction	8.8	0.049

Table 2: Results of multivariate logistic regressions.

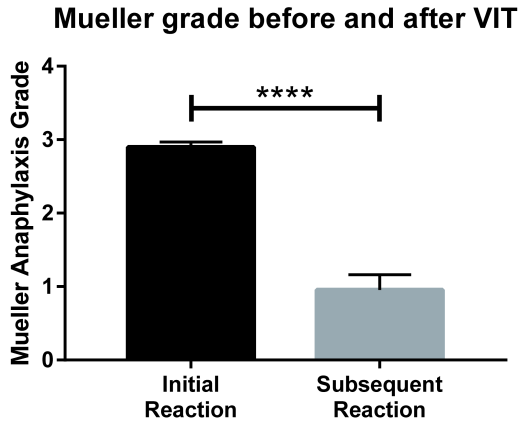
Journal Pre-proof

Journal Pre-proof

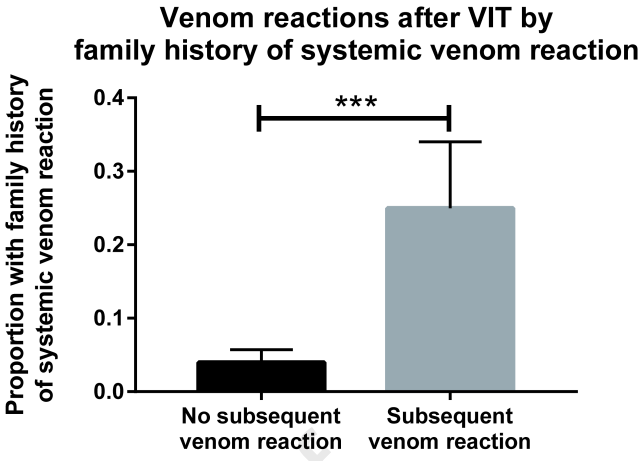
Mastocytosis in HVA



Journal Pre-proof

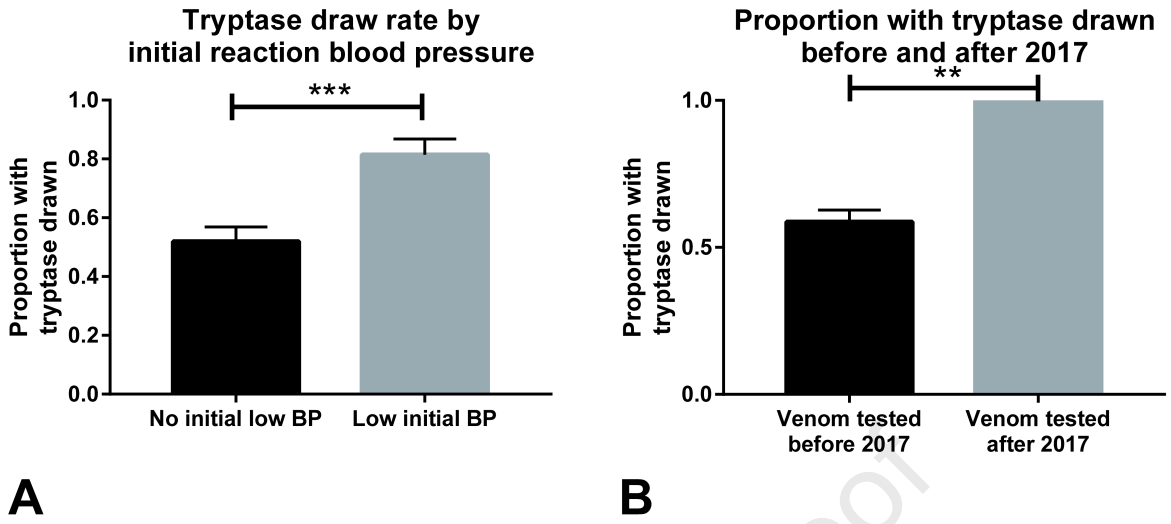


A



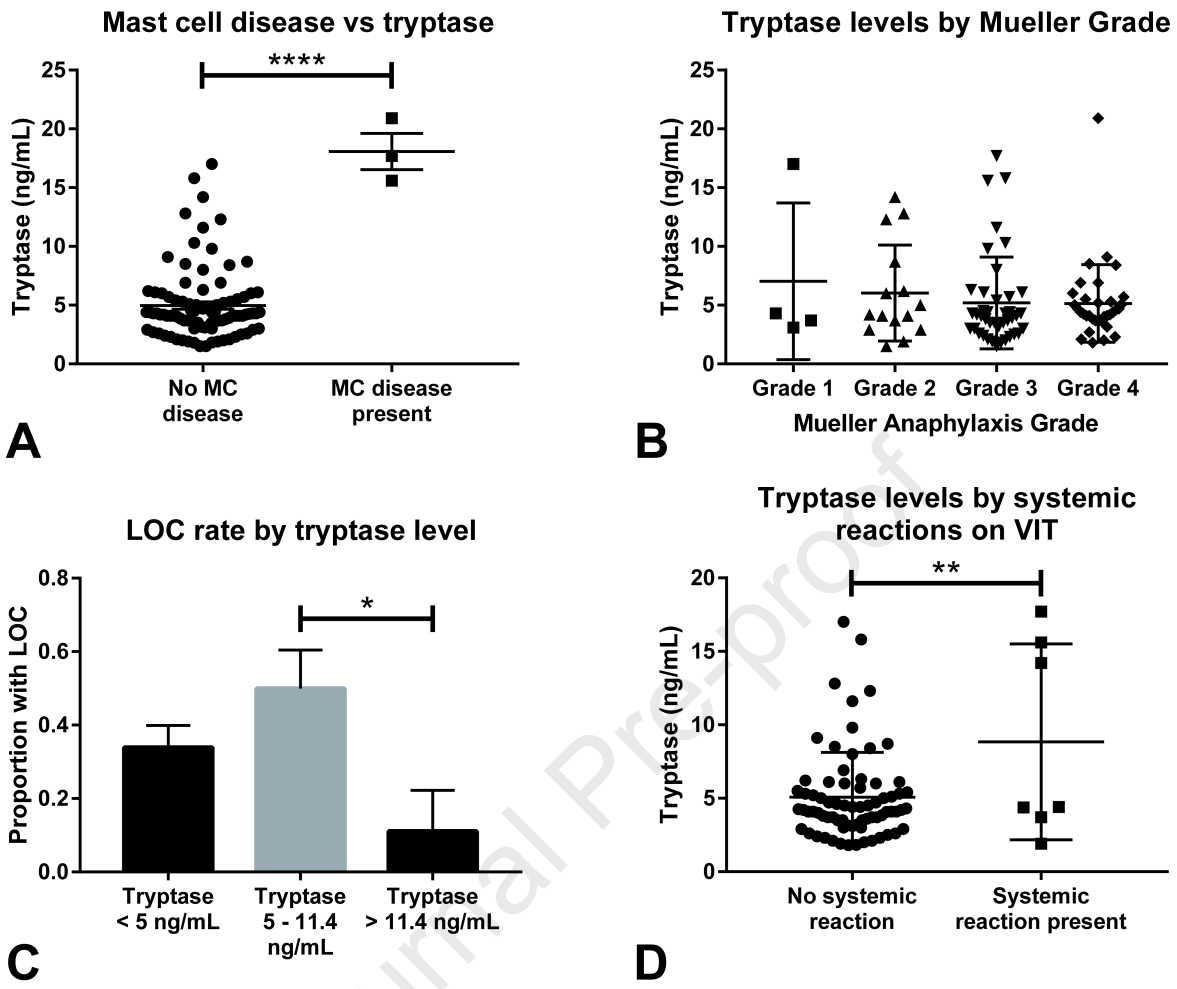
B

Journal Pre-proof



A B

Journal Pre-proof



Journal Pre-proof