To the Editor,

Common variable immunodeficiency (CVID) is a primary immunodeficiency syndrome resulting in recurrent infections along with increased susceptibility to malignancy and autoimmunity [1]. Up to 20-40% of patients with CVID develop autoimmune hematological disorders, with immune thrombocytopenic purpura (ITP) being the most frequently reported manifestation [2]. The mechanism of autoimmunity in CVID is incompletely understood but is thought to be secondary to the lack of switched memory B cells, failure of removal of self-reactive B cells as well as abnormalities in B and T cell interaction [3]. Although cytopenias such as autoimmune hemolytic anemia (AIHA) and ITP can precede the diagnosis of CVID [2,4,5,6], it is unknown how many patients presenting with these cytopenias have undiagnosed CVID, a condition where there is commonly a delay in diagnosis, particularly in adults [7]. To help answer this, we performed a retrospective cohort study with the primary objective of identifying the prevalence of CVID in patients hospitalized with ITP.

With the approval of Rochester Regional Health's Institutional Review Board (IRB), we used the International Classification of Diseases Tenth Revision (ICD-10) codes to identify patients admitted at Rochester General Hospital between January 1st, 2016 to December 31st, 2018 requiring treatment for acute ITP, or community-acquired pneumonia (CAP) while having previously documented history of ITP. Patients <18 years of age or those with pregnancy-related or drug-induced ITP were excluded. For eligible patients, we reviewed the electronic medical record (EMR) from the time of index hospitalization to November 2020 to determine whether a diagnosis of CVID was later established. The diagnosis of confirmed CVID was defined as a marked decrease total in IgG (>2 standard deviation below normal age-adjusted level) and IgA

titers with or without low total IgM level in the absence of secondary causes of hypogammaglobulinemia (e.g., the use of anti-CD20 therapies or hematologic malignancies, etc) and having a documented poor antibody response to at least one vaccine (i.e., the absence of protective levels of antigen-specific IgG titers four weeks post vaccination) [8,9]. Probable CVID was defined as total IgG titer >2 SD below normal age-adjusted level and IgA titers with or without low total IgM levels in the absence of secondary causes of hypogammaglobulinemia [8]. All patients with admitted with acute ITP had a >50% decrease from their baseline platelet count and were identified to have ITP by a board-certified hematologist. All patients admitted with CAP who had a prior history of ITP also had documentation in the chart of ITP confirmed by a board-certified hematologist.

Forty-nine unique patient admissions met the inclusion criteria within the three-year study period (Figure 1). Eight of the 49 patients (16%) had CAP with an established history of ITP. All patients admitted with acute ITP (n=41) had at least moderate ITP defined as platelet count between 50,000 to 100,000 u/l. Thirty-seven of these patients had severe ITP defined as a platelet count of less than 10,000 u/l. Patients with a previous history of ITP who were admitted with CAP either had moderate thrombocytopenia or mild thrombocytopenia defined as platelet count >50,000 u/l but less than 150,000 u/l. Half of these patients (n=4) were on low dose oral prednisone daily for chronic ITP. The median age of the cohort was 68 (IQR 57-82) years of age. Twenty-four patients (49%) were females. Thirty patients (61%) were treated with intravenous immunoglobulin (IVIG) therapy. Four patients (8%) had their immunoglobulin (Ig) levels checked on index hospitalization, while 11 patients (22%) had their Ig levels checked since the index hospitalization to November 2020. Three patients (6%) were identified to have laboratory evaluation concerning for CVID (Table 1).

The first patient was a 35-year-old female with a history of ITP diagnosed at age 29 with a nadir platelet count of <10,000/uL requiring IVIG treatment previously. She had two episodes of rhinosinusitis within the past year requiring outpatient antibiotic therapy before being admitted for sepsis from CAP requiring oxygen support. IgG at the time of admission was less than 400 mg/dl and she was referred to Allergy/Immunology on discharge for a complete immune evaluation, where she was diagnosed with confirmed CVID at age 35 due to low IgG, low IgM, and poor response to vaccines, particularly Pneumovax (PPV23).

The second patient was a 37-year-old female who was admitted with uncomplicated pyelonephritis and thrombocytopenia due to acute ITP with a platelet count of 57,000 uL. She was hospitalized twice in the previous two years for CAP, prompting immune screening that revealed undetectable levels of IgG, IgA, and IgM. She did not respond to PPV23 was therefore diagnosed with confirmed CVID two months later and started therapy with intravenous immunoglobulin (IVIG).

The third patient was a 53-year-old female with a history of ITP diagnosed at age 50 and end-stage renal disease on peritoneal dialysis who was admitted hypoxic respiratory failure thought to due to volume overload and superimposed CAP. The platelet count on admission was 18,000/uL. Her hospital stay was complicated by peritonitis resulting in severe septic shock secondary to peritoneal dialysis catheter placement. Immune evaluation revealed significantly low IgG, IgM, and IgA titers highly suggestive of probable CVID, but a complete evaluation was not completed because the family opted for comfort care.

Our results mirror previous studies that have described a subset of patients with CVID who present with autoimmune, rather than infectious complications. In a retrospective chart review of 326

patients with CVID by Wang et al., fifteen patients (4.6%) had ITP. Of those 15 ITP patients, nine patients had an episode of ITP before the diagnosis of CVID [4]. Similarly, in a prospective study of 224 patients with CVID, 5.6% had a concurrent diagnosis of ITP. [5] In a small study of 21 CVID patients, 62% of patients had an episode of ITP within six months before being diagnosed with CVID [6]. Early recognition of CVID has important therapeutic implications, especially in patients who require long-term immunosuppressive therapies such as danazol, mycophenolate, and rituximab, all of which may increase the risk of life treating infections in patients with unrecognized CVID [6,10,11]. Furthermore, it is also important to evaluate for CVID in cases of ITP requiring splenectomy, as the routine administration of pre-operative vaccinations would likely not lead to an adequate immune response in patients with CVID [11].

Our study has important limitations, most notably a small sample size and short follow-up period. We also screened for eligible patients through inpatient hospitalization records and therefore did not include a considerable number of patients with ITP that were managed as outpatients. Despite these limitations, we feel our results address an unmet need for screening for CVID in adult patients admitted with ITP.

In conclusion, physicians should be aware of ITP as an autoimmune manifestation that may precede the classical infectious complications of CVID. Larger studies with longer follow up are needed to determine the prevalence of occult CVID among patients with ITP. Nevertheless, studies to date suggest that clinicians should screen for CVID in patients with ITP, particularly those with a history of CAP requiring hospitalization, since early detection of CVID may lead to the prevention of recurrent infections and other complications.

Conflict of Interest: The authors declare that they have no known competing personal or financial interests.

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Figure 1: Description of the study population

*Includes patients who had their IgG level checked on index hospital and those who had it checked between index hospitalization to November, 2020.

Table 1: Summary of patients diagnosed with confirmed and probable common variable immunodeficiency syndrome.

F: female, CAP: Community acquired pneumonia, CVID: common variable immunodeficiency syndrome/

* Platelet count nadir at the time of diagnosis of immune thrombocytopenic purpura

** An adequate response to Streptococcus pneumoniae; PPV23 vaccine was defined as a two-fold increase from baseline if pre-vaccination specific IgG were ≥1.3 mcg/ml, or if titers increased by four-fold from baseline if pre-vaccination specific IgG were < 1.3 mcg/ml, for > 70% of the pneumococcal serotypes [9].

Reference ranges: IgG: 700 - 1600 mg/dl, IgA: 70 - 400 mg/dl, IgM: 50 - 300 mg/dl