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BACKGROUND

- Febrile Non-Hemolytic Transfusion Reactions (FNHTRs) are acute transfusion complications resulting in fever, chills, headache, nausea, and/or vomiting<sup>1</sup>;
- FNHTR is one of the most frequent transfusion complications that may exacerbate underlying comorbidities and result in transfusion interruption and prolonged hospitalization<sup>1</sup>;
- Older and immunocompromised (IC) recipients may be at an increased risk for FNHTR due to higher likelihood of prior alloimmunization (e.g., transfusion, pregnancy) and increased demand for blood<sup>1-5</sup>.

OBJECTIVES

**To assess FNHTR occurrence and potential recipient and transfusion risk factors among the U.S. Medicare population ages 65 and older transfused in the institutional outpatient setting, During 2016-2023**

METHODS

- **This is a retrospective cohort claims-based study using Medicare claims databases from April 1, 2016, through December 2, 2023:**
  - ⇒ Procedure and revenue center codes were used to identify transfusion of blood components, and revenue center units were used to quantify blood transfused;
  - ⇒ Outpatient transfusion visits were used as the unit of analysis and each visit comprised transfusions on the same date;
  - ⇒ FNHTR was ascertained via diagnosis code(s) recorded on the same or next day of outpatient transfusion visit;
  - ⇒ Outpatient transfusion visits were grouped into mutually exclusive blood component categories: RBCs only, platelets only, plasma only, and multi-component transfusions.
- **We assessed unadjusted FNHTR rates per 100,000 outpatient transfusion visits: overall, by calendar year, IC status, demographics, 6-month history of health conditions (using Elixhauser Comorbidities), blood components (including processing), and number of units transfused; and**
- **We compared IC vs. non-IC visits and IC vs. non-IC cases (i.e., visits with FNHTR) by demographics, health conditions, hospitalization, ICU/CCU admission, inpatient mortality and length of stay (LOS).**
- **We assessed outcome trends by calendar year, age, and number of units transfused.**

RESULTS

- **Of 3,360,771 outpatient transfusion visits during the 2016-2023 study period, 574 had a FNHTR diagnosis recorded:**
  - ⇒ **Overall FNHTR rate of 17.1 per 100,000 transfusion visits (95% CI: 15.7-18.6), with annual rates ranging from 16.0 (12.6-20.2) in 2016 to 12.8 (9.5-17.2) in 2023, p<0.001 (Figure 1):**
    - Pre-pandemic (2016-2019) vs. during COVID-19 pandemic (2020-2023) rates were 22.0 (19.9-24.3) vs. 11.5 (9.9-13.3);
    - Pre- vs. pandemic distribution (%) of outpatient visits with 1 and 2+ units transfused was: 40.8% vs. 54.5% and 59.1% vs. 45.4%, respectively;
    - FNHTR rate for transfusion visits with COVID-19 recorded was 9.3 (0.5-60.6) or with history of COVID-19 was 12.2 (7.2-20.3);
    - IC vs. non-IC rates: 19.7 (18.0-21.5) vs. 9.9 (8.0-12.3);
    - 84.5% of FNHTR cases were IC and 16.6% of all FNHTR cases were hospitalized with 28.4% ICU/CCU admission and 24.2% LOS≥7 days;
  - ⇒ **FNHTR rates differed by patient demographics and health conditions:**
    - Males vs. females: 22.9 (20.7-25.3) vs. 10.7 (9.2-12.4);
    - Whites vs. non-whites: 17.2 (15.7-18.8) vs. 16.4 (12.9-20.7);
    - Rates varied by age groups, with no trend by age overall and by IC status (p>0.05) (Figure 2);
    - FNHTR rates varied by measured comorbidities, with the highest rates identified with histories of weight loss, lymphoma, coagulopathy, and other neurological disorders (Table 1);
  - ⇒ **Rates varied by transfusion characteristics:**
    - **With vs. without six-month transfusion history:** 18.7 (17.1-20.5) vs. 11.8 (9.6-14.5);
    - **Rates by blood components:** plasma only [5.3 (0.9-21.4)], RBCs only [9.9 (8.8-11.2)], platelets only [25.6 (21.2-30.7)], and multi-component transfusions [79.3 (68.8-91.5)] mostly comprised of RBCs and platelets (Figure 3);
    - **For Platelets-only visits, the highest rates by component processing (Figure 4) were for:** whole-blood (WB)-derived platelets only [39.4 (19.2-77.7)], pathogen-reduced (PR) platelets only [40.8 (28.7-57.6)], and non-leukoreduced (NLR) non-irradiated (NIR) platelets only [79.4 (13.7-319.6)];
    - Overall, 19.7% of apheresis platelets-only visits had PR platelet transfusions, with 20.1% for IC and 13.7% for non-IC (data not shown);
    - **For RBC-only visits, the highest rate by component processing** was 14.4 (7.0-28.4) for NLR NIR RBCs (Data not shown);
    - **Rates by number of units transfused ranged** from 13.5 (11.8-15.4) for 1 unit to 26.8 (11.7-57.9) for ≥5 units (p<0.001);
  - **Differences were identified when comparing IC vs. non-IC transfusion visits, and IC vs non-IC cases:**
    - ⇒ **IC transfusion visits were more likely to be:**
      - Males (56.0% vs. 42.3%) and Ages 65-79 (67.1% vs. 53.7%);
      - With prior transfusions (85.6% vs. 50.4%);
    - ⇒ **IC cases were less likely to be hospitalized the same or next day (14.6% vs. 27.0%);**
    - ⇒ **Among those hospitalized, IC cases were less likely to be admitted to ICU/CCU (25.4% vs. 37.5%); and to have LOS ≥7 days (22.5% vs. 29.2%).**

RESULTS

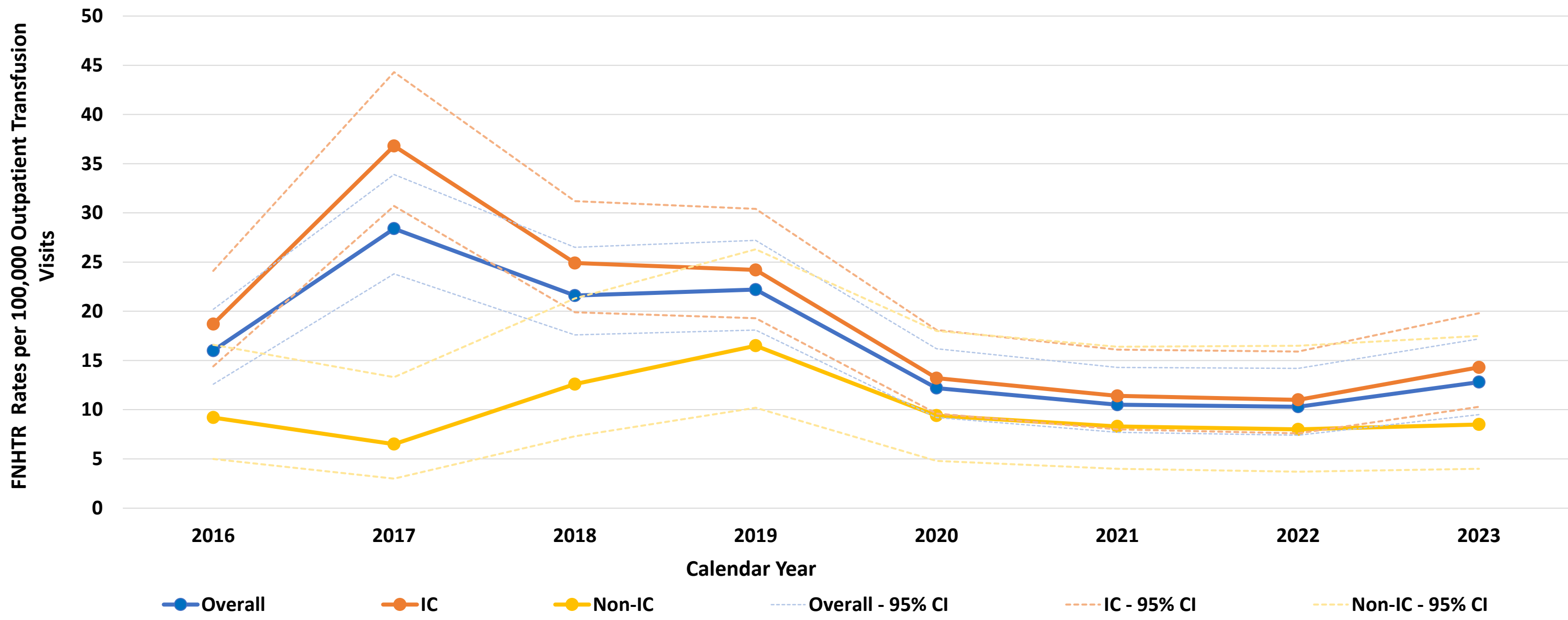


Figure 1. Unadjusted FNHTR Rates by Calendar Year, Overall and by IC Status, During 2016-2023

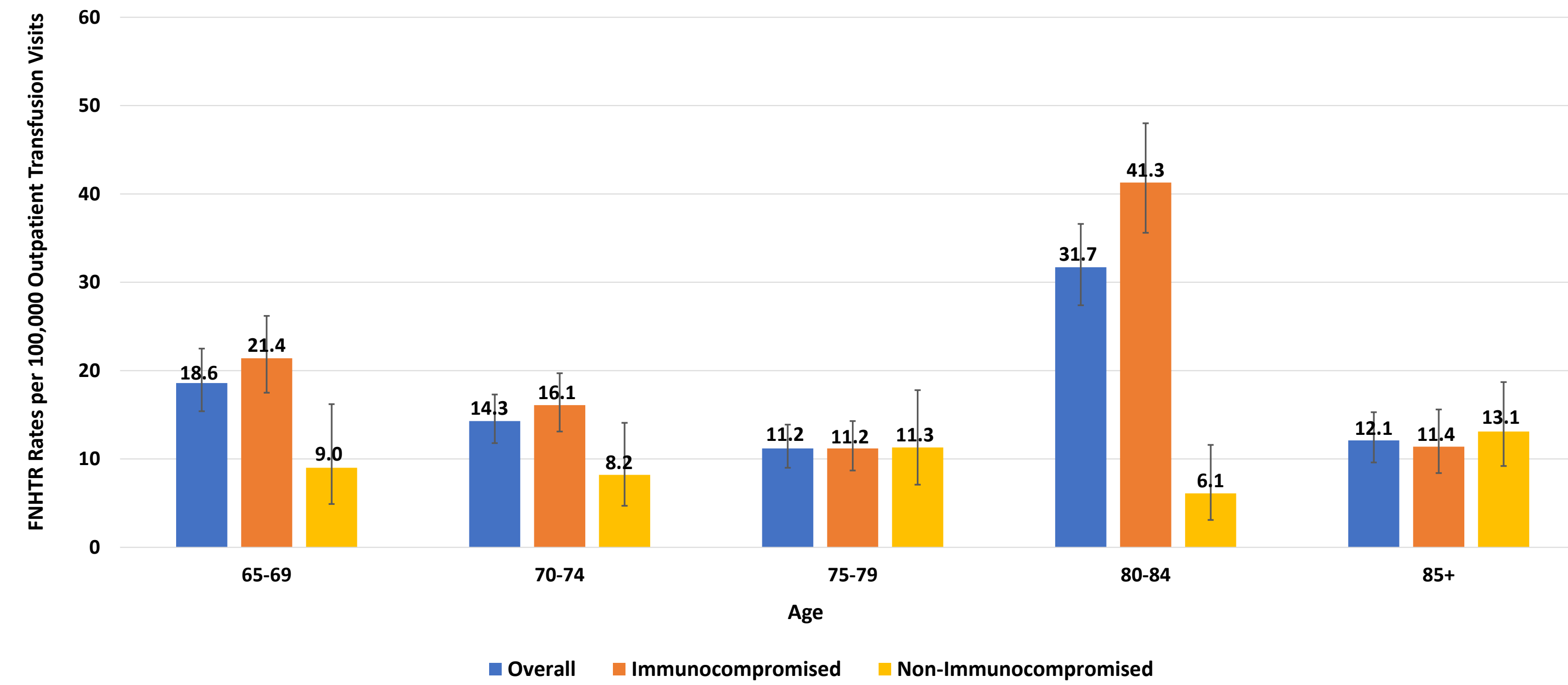


Figure 2. Unadjusted FNHTR Rates by Age, Overall and by IC Status

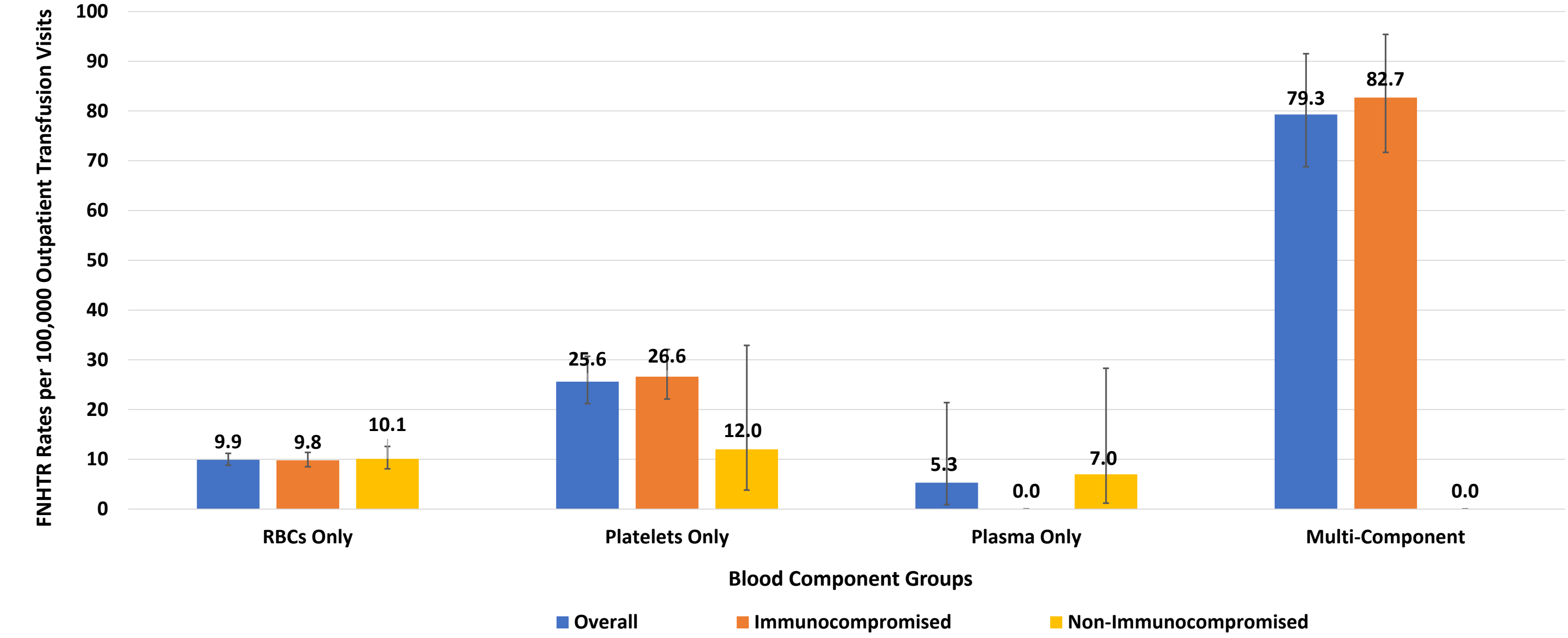


Figure 3. Unadjusted FNHTR Rates by Blood Component Groups, Overall and by IC Status

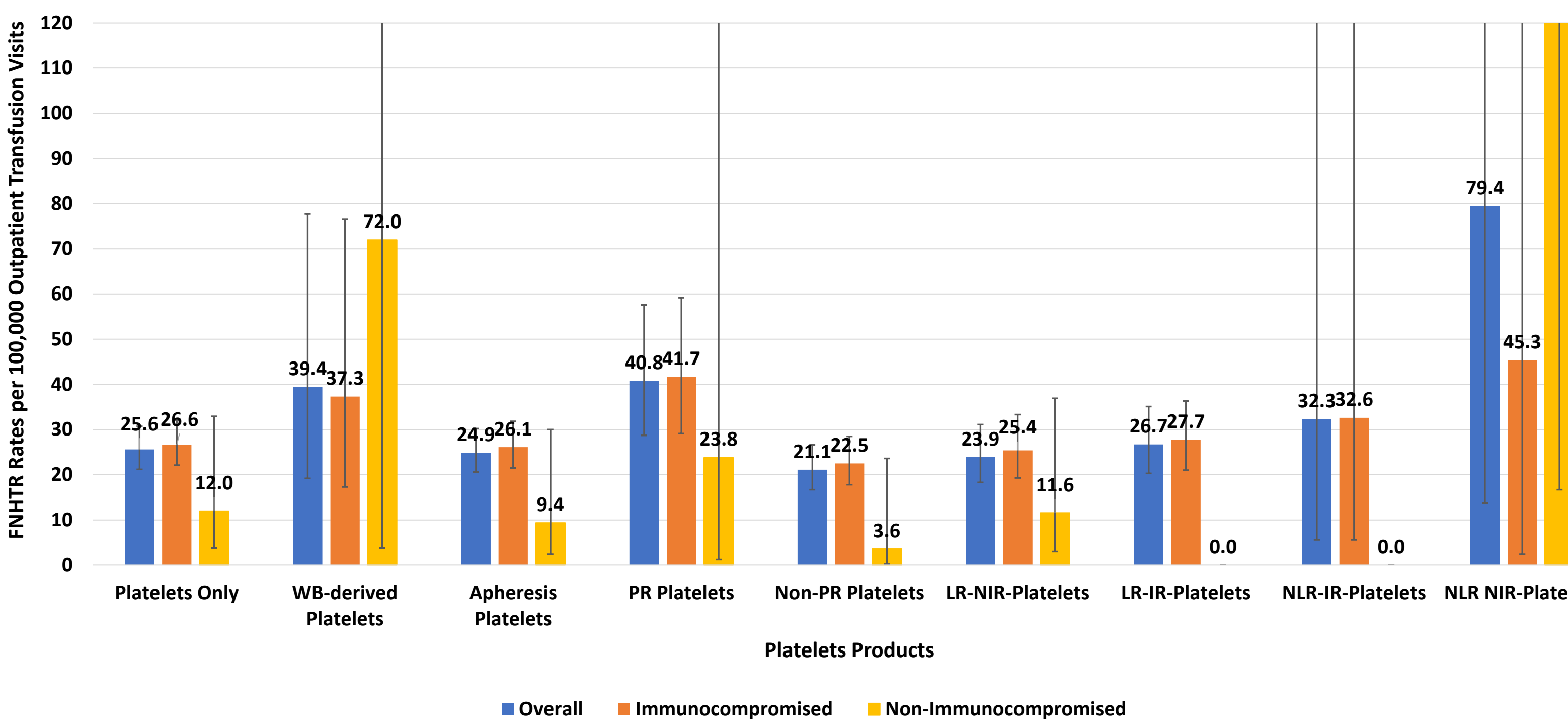


Figure 4. Unadjusted FNHTR Rates for Platelets-only Visits by Processing Method, Overall and by IC Status

Table 1. Unadjusted FNHTR Rates by Six-month History of Underlying Health Conditions, Overall and by IC Status

Health Conditions	Overall	IC	Non-IC
All Transfusion Visits	17.1 (15.7-18.6)	19.7 (18.0-21.5)	9.9 (8.0-12.3)
Weight Loss	21.1 (17.8-25.0)	23.1 (19.2-27.7)	13.5 (8.2-21.8)
Lymphoma	20.5 (16.7-25.0)	20.7 (16.9-25.3)	-
Coagulopathy	20.2 (18.0-22.6)	21.6 (19.2-24.3)	9.3 (5.5-15.4)
Other Neurological Disorders	19.2 (15.4-23.8)	22.7 (17.8-28.9)	11.1 (6.5-18.8)

*Note: This table displays the four health conditions with highest overall FNHTR rates. "-" indicates no outcomes were observed.*

DISCUSSION AND CONCLUSIONS

**Our population-based nationwide study on FNHTR occurrence in outpatient elderly shows:**

- Overall FNHTR occurrence trends varied over time, overall and by IC status:**
  - Lower rates during pandemic vs. pre-pandemic, overall and by IC status, which may be related to lower blood utilization during pandemic and needs further investigation;
  - There were significantly declining annual trends overall and for IC (p<0.001) and no trend found for non-IC;
  - Further studies are needed to better understand the differences in outcome trends by IC status;
- FNHTR rates are higher for IC vs. non-IC beneficiaries, which could be related to higher risk of prior alloimmunization as well as differences in blood component utilization (e.g., higher platelets use), underlying comorbidities and demographics;**
- IC vs. non-IC had lower case-severity (e.g., lower hospitalization rate), which may be related to differences in immune function and patient characteristics (e.g., IC were younger);**
- FNHTR rates are likely related to the blood components transfused:**
  - Higher FNHTR rates were found for platelets-containing groups, with the highest risk for multi-component visits mostly comprised of RBCs and platelets;
  - Among platelets-only visits, the highest unadjusted rates by component processing were identified for: whole-blood-derived platelets, pathogen-reduced platelets, and NLR NIR platelets;
  - Significantly higher FNHTR risk was identified for pathogen-reduced vs. non-pathogen-reduced apheresis platelets, overall and for IC;
- Greater number of units transfused and recorded prior alloimmunization (i.e., history of transfusions) were associated with significantly increased risk of FNHTR, overall and for IC beneficiaries;**
- Demographic characteristics and underlying comorbidities may contribute to FNHTR occurrence and require additional research:**
  - Highest FNHTR rates by age were found for ages 65-69 and 80-84, overall and for IC beneficiaries;
  - Higher rates for Males vs. Females were identified, overall and for IC (data not shown);
- Further investigations using adjusted analyses are needed to better understand FNHTR risk factors overall, by pandemic, COVID-19 and IC status as well as the outpatient blood utilization during vs. pre-pandemic.**

STRENGTHS AND LIMITATIONS

**Strengths:**

- **This is the largest population-based assessment of FNHTR occurrence trends and potential risk factors among the U.S. elderly transfused in the institutional outpatient setting;**
- **This study highlights the utility of large Medicare databases;**

**Limitations:**

- **Evaluation was based on the administrative databases, and consequently:**
  - ⇒ FNHTR occurrence may be under- or mis-recorded (i.e. unknown sensitivity and specificity of diagnosis codes in the claims data);
  - ⇒ Potential under- or mis-recording of transfusion procedures and number of units;
  - ⇒ Clinical detail is not available to validate FNHTR diagnosis recorded;
- **Unadjusted rate comparisons may produce biased results, and thus require adjustment for potential confounders.**

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