Supporting Information 8: Derivation of IME scores (D, Q, C, L, I, N)

We designed a quality assessment and data extraction tool, which included domains to capture information on study design (D) and quality of reporting (Q); confidence of comorbidity diagnosis (C); likelihood of a causal link between comorbidity and ITP (L); confidence of ITP diagnosis (I); and the number of patients with a given comorbidity (N).

Score D

Score D was assessed after positing the question: Does the study ask whether a comorbidity or drug/vaccine induces (or is associated with) ITP as part of its hypothesis or specific aims/objectives, OR is the question that a comorbidity or drug/vaccine induces (or is associated with) ITP answered by study design? If the answer was *yes*, a D score was assigned; if the answer was *no*, the study was designated "Descriptive Association Only" for that comorbidity and assigned an arbitrary point of 1. A "'Retrospective case series or case report" was assigned 2 points; a "Cross-sectional study" was given 3 points; a "Retrospective cohort or case-control study" was assigned 4 points; both "Prospective case-control study" and "Prospective cohort study" were given 5 points; an "'Unblinded randomized or non-randomized control trial or experiment" was assigned 6 points; and a "'Blinded randomized or non-randomized control trial or experiment" was assigned 7 points. Most of the comorbidities fell under "Descriptive Association Only" and there was only 1 study that scored 7 points under "'Blinded randomized or non-randomized control trial or experiment" design. Score D was derived by normalizing the assigned points (divided by 7, the maximum value).

Score Q

Score Q was assessed by evaluating 13 questions regarding the general quality of reporting of the study. Q1: Is (are) the study hypothesis (hypotheses) that a comorbidity or drug/vaccine induces (or is associated with) ITP clearly stated, OR is the question that a comorbidity or drug/vaccine induces (or is associated with) ITP clearly answered by study design? Q2: Is (are) the specific aim(s) / objective(s) of the study clearly stated AND does at least one aim/objective include a means to identify whether a comorbidity or drug/vaccine induces (or is associated with) ITP? Q3: Multi-center? Q4: Clear inclusion / exclusion criteria? Q5: Data on cases screened / excluded? Q6: Search terms described? Q7: Disease heterogeneity? Q8: Clear outcome measure definition? Q9: Clear presentation of results? Q10: Appropriate statistical testing? Q11: Variability measure reported (SD, range, interquartile range)? Q12: Conclusions supported by results? Q13: Clear conflict of interest statement?

Answers to Q1-Q6 and Q8-Q13, were either "'No / absent / unclear / NA" (assigned 0 points), "Partially reported / suggested" (assigned 1 point) or "Yes" (assigned 2 points). For disease heterogeneity assessment in Q7, 2 points were given for "High," in which cases recruited were all peracute or acute in clinical presentation and evolution, one disease (e.g. ITP); subacute or chronic in clinical presentation and evolution, one disease (e.g. ITP); or disease of disparate nature, but analyzed in separate, homogeneous groups (e.g. one disease, acute vs chronic; or several different diseases, with segregation of severity within each disease group); 1 point was given for "Intermediate," in which stratification was

suggested but details were not explicitly stated; and 0 points were given for “Low,” relating to all other references to disease heterogeneity.
The general quality of reporting of the study was weighted according to our assessment of relative importance of these specific questions. A weighted sum of these 13 questions was then computed as:
2*Q1+2*Q2+Q3+Q4+Q5+Q6+2*Q7+2*Q8+3*Q9+3*Q10+2*Q11+3*Q12+Q13
(For *Descriptive Association Only*, general study quality (Q) was irrelevant to the question of the causal relationship between comorbidity and ITP, and was therefore given 0 points.) Score Q was then derived by normalizing the weighted sum (divided by 43, the maximum value in this dataset).

Score C
Score C assessed the confidence of comorbidity diagnosis. For infectious disease, “Direct detection (culture, cytology, PCR)” was given 3 points, “Serology” was given 2 points, and “All other references to infection” was given 1 point; for cancer, “Consistent lesion with cytology or histopathology confirmation” was given 3 points, “Consistent lesion without cytology or histopathology confirmation” was given 2 points, and “All other references to neoplasia” was given 1 point; for sepsis, ”Presence of systemic inflammatory response syndrome (SIRS) as defined by established criteria with confirmed bacterial infection” was given 3 points, “Presumed SIRS with compatible clinicopathological or imaging findings , but without explicit statement of SIRS criteria and/or bacterial culture results” was given 2 points, and “All other references to sepsis” was given 1 point; for inflammatory disease, “Confident diagnosis” on the basis of definitive information derived from discrete observations or the fulfilment of accepted diagnostic criteria was given 3 points, and “All other references to infection” was given 1 point; for drugs, “Drug administered for a continuous period of at least 7 days within a 28-day period prior to presentation” was given 3 points, “Drug administered within a 28-day period prior to presentation but details not explicitly stated” was given 2 points, and “All other references to drugs” was given 1 point; for toxin, “Verified toxin exposure: at least 1 documented occurrence within a 28-day period prior to presentation” was given 3 points, “Toxin exposure suspected within a 28-day period but details not explicitly stated” was given 2 points, and “All other references to toxins” was given 1 point; for vaccines, “Vaccine administered within 28 days prior to presentation” was given 3 points, “Vaccine within 28 days, no details” was given 2 points, and “All other references to vaccines” was given 1 point. Score C was then derived by normalizing the assigned points (divided by 3, the maximum value).

Score L
Score L assessed the likelihood of a causal link between comorbidity and ITP, and each comorbidity was assigned either “'No / absent / unclear / NA” (1 point), “Partially reported / suggested” (2 points) or “Yes” (3 points). Score L was derived by normalizing the assigned points (divided by 3, the maximum value).

Score I
Score I assessed the confidence of ITP diagnosis, and was assigned either “Possible Secondary/Associative ITP” (1 point), “Possible Secondary/Associative ITP with Immunologic Evidence” (1.5 point) “Probable Secondary/Associative ITP” (2 points) or “Probable Secondary/Associative ITP with Immunologic Evidence” (3 points). No score (0) was assigned

if ITP was unlikely, the diagnosis could not be determined, or ITP was primary (non-associative) in nature. Score I was derived by normalizing the assigned points (divided by 3, the maximum value).

Score N

Score N accounted for the number of patients with a given comorbidity, and was given 1 point (1 patient), 2 points (2 to 5 patients), 3 points (6 to 10 patients), 4 points (11 to 20 patients, or 5 points (21 to 50 patients). Score N was derived by normalizing the assigned points (divided by 5, the maximum value).

The integrated metric of evidence (IME) value was computed as the sum of the normalized scores, weighted according to our assessment of relative importance to evidence rating, so long as only that comorbidity was present in individual patients; hence, IME=2D+Q+C+2L+I+N. Threshold IME values were computed to allow comorbidities to be designated as negligible, low, intermediate, or high evidence for a causal relationship with ITP. The threshold between negligible and low evidence was taken to be a hypothetical *Descriptive Association Only* study, with intermediate C, L, and I scores, and 1 positive case (IME=3.15). The threshold between low and intermediate evidence was taken to be a hypothetical cross-sectional study, with a Q score of 28, intermediate C, L, and I scores, and 2 to 5 positive cases (IME=4.57). Finally, the threshold between intermediate and high evidence was taken to be a hypothetical prospective cohort/case-control study, with a Q score of 28, high C score, intermediate L score, high I score (*Probable Secondary/Associative ITP with Immunologic Evidence*), and 2 to 5 positive cases (IME=5.81).