Japanese Journal of Gastroenterology and Hepatology[R] ISSN 2435-1210 | Volume 11

Clinical Image Open Access

A Non-Invasive Integrated Model for Accurate Preoperative Identification of the Aggressive Macro Trabecular-Massive Subtype of Hepatocellular Carcinoma

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Received: 10 Jan 2026
Accepted: 22 Jan 2026
Published: 14 Feb 2026
J Short Name: JJGH

Keywords:

Liver; Macrotrabecular-Massive Hepatocellular Carcinoma; Contrast-Enhanced Ultrasound; Reoperative Prediction; Diagnosis

Citation:

Fang Nie, A Non-Invasive Integrated Model for Accurate Preoperative Identification of the Aggressive Macro Trabecular-Massive Subtype of Hepatocellular Carcinoma. Japanese Jour of Gastro and Hepatology® 2026; V11(1): 1-9

1. Abstract

Gastrointestinal (GI) manifestations after coronavirus disease 2019 (COVID-19) vaccination have emerged as a frequent concern during global vaccine rollout. Although most symptoms are mild and transient (nausea, vomiting, diarrhea, abdominal pain). Rare but serious GI-related manifestations-such as autoimmune hepatitis (AIH), acute abdomen, pancreatitis, and vaccine-induced immune thrombotic thrombocytopenia (VITT)-have been documented in case reports and small series. Population-level studies generally show no strong causal increase in severe GI events, although certain conditions like VITT are mechanistically established. These findings highlight the importance of distinguishing common reactogenic symptoms from uncommon immune-mediated conditions, emphasizing careful clinical assessment, timely recognition of red-flag presentations, and ongoing pharmacovigilance to clarify true risks in diverse populations.

2. Introduction

This review synthesizes clinical-trial safety data, pharmaco-vigilance reports, cohort and registry studies, and recent systematic reviews and case series published since vaccine rollout. The focus is on (a) common, self-limited gastrointestinal (GI) adverse events (AEs) [1-5]; (b) specific, less common GI pathologies reported after vaccination (appendicitis, acute abdomen, pancreatitis, autoimmune hepatitis (AIH), splanchnic venous thrombosis) [6-9,18-20]; and (c) biological plausibility and clinical implications [11-26,18]. The objective is to clarify whether coronavirus disease 2019 (COVID-19) vaccination is associated with GI manifestations and to identify which events have epidemiologic support versus those supported mainly by isolated case reports [7,10,11,15,19]

3. Common GI Complaints After Vaccination - Frequency & Clinical Course

Across randomized trials and post-marketing surveillance, nausea, vomiting, diarrhea, abdominal pain, anorexia, dyspepsia, heartburn, bloating, and flatulence are consistently among the most reported GI AEs following COVID-19 vaccination [1-5,14]. These symptoms typically begin within 0-72 hours of vaccination and resolve in a few days; they are considered reactogenic symptoms reflecting innate immune activation rather than organ-specific injury [2,11,15,18]. Most symptoms resolve spontaneously within a few days and do not require medical intervention beyond supportive care [1-4,7]. Variability in symptom frequency between vaccine platforms has been reported, influenced by vaccine type, sex, age, prior COVID-19 infection, and psychosocial factors such as nocebo responses [2,4,14,5,31]. Current evidence indicates that common GI symptoms are expected, self-limited, and do not indicate long-term pathology [11,16,1,9].

4. Specific GI Conditions Reported After COVID-19 Vaccination

4.1. A. Appendicitis

Early post-marketing signal-detection analyses suggested a possible increase in appendicitis following mRNA vaccination [11,1,3]. However, subsequent large-scale population studies-such as na-

tional registry analyses-have not demonstrated a statistically significant increase in appendicitis incidence after vaccination [10,11,21]. Most evidence supports a temporal but not causal relationship, and appendicitis should be managed based on standard clinical presentation rather than presumed vaccine association [2,3,9].

4.2. B. Acute Abdomen / Surgical Presentations

Case reports and small case-series have described acute abdomen presentations (appendicitis, cholecystitis, pancreatitis, diverticulitis) temporally following vaccination [1,7,13]. Systematic reviews of these case reports conclude that most cases are isolated and do not establish causality [7,18,19]; publication and reporting bias (tendency to publish unusual post-vaccine events) likely inflate apparent associations. The large cross-sectional dataset showed only 2.9% requiring hospitalization for any adverse event, illustrating the rarity of severe GI pathology [22,7,9]. Nonetheless, severe abdominal pain after vaccination warrants prompt evaluation (imaging and labs) to exclude surgical or vascular emergencies [2,3,11].

4.3. C. Autoimmune Hepatitis (AIH) and other Immune-Mediated Hepatitis

There are multiple case reports and small case series of AIH-like hepatitis occurring days to weeks after various COVID-19 vaccines (mRNA and adenoviral), often presenting with jaundice, markedly elevated liver enzymes, and positive autoimmune markers [18,7,14]. Histology in many reports shows interface hepatitis and plasma-cell infiltrates akin to idiopathic AIH; some patients responded to corticosteroids [7,9]. However, larger pharmacovigilance and population-level studies have not demonstrated a clear increase in AIH incidence attributable to COVID-19 vaccination, and analyses of VAERS data do not suggest a population-level safety signal. Thus, while vaccine-triggered AIH may occur rarely in predisposed individuals, current evidence supports that it is an uncommon event and that causality remains uncertain [15,16,9]. Clinicians should consider standard workup (LFTs, autoimmune serologies, viral hepatitis panel, and liver biopsy when indicated) when encountering unexplained hepatitis after vaccination [2,5,25].

4.4. D. Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT) and Splanchnic Thrombosis

VITT is a rare, well-described syndrome linked primarily to adenoviral-vector COVID-19 vaccines (e.g., ChAdOx1/AstraZeneca, Janssen) characterized by thrombosis at unusual sites (cerebral venous sinuses, splanchnic veins) together with thrombocytopenia and anti-PF4 antibodies. Splanchnic (mesenteric or portal) venous thrombosis can present severe abdominal pain, nausea, vomiting, or GI bleeding and requires urgent recognition because management differs from typical venous thrombosis (avoid heparin until VITT excludes [2,6,7,9,27]; use non-heparin anticoagulants and IVIG in many cases) [9,27-31]. This is one of the clearest specific GI-relevant vaccine associations and is rare but serious.

4.5. E. Pancreatitis and Other Pancreaticobiliary Events

Isolated case reports have described acute pancreatitis after vaccination, but robust epidemiologic evidence linking vaccines causally to pancreatitis is lacking. Standard diagnostic workup for pancreatitis should be followed, and alternative causes (gallstones, alcohol, hypertriglyceridemia, medications) should be excluded.

4.6. F. Inflammatory Bowel Disease (IBD) Flares

Patients with IBD were a major population of interest during vaccination campaigns. Large cohorts and meta-analyses indicate that COVID-19 vaccination is not associated with increased risk of severe IBD flares or long-term disease worsening; transient symptom increases are possible but uncommon [1,2,3]. Vaccination is strongly recommended for patients with IBD, given their risk from COVID-19 infection [18,5,9].

4.7. G. Differential Causality Assessment

Reinforcement of contrast (Emphasis on VITT): Crucially, for most severe GI events reported in case series (AIH, appendicitis, pancreatitis, acute abdomen), population studies have not shown clear, consistent increases attributable to vaccination. Therefore, these remain temporally associated but unproven as vaccine caused. This stands in direct contrast to VITT, which is an important exception where mechanistic and epidemiologic evidence strongly links the adenoviral-vector vaccines to the syndrome. 4. Biological plausibility proposed mechanisms

Innate Immune Activation accounts for most common and transient GI discomfort. In sharp contrast, VITT (Vaccine-Induced Thrombosis and Thrombocytopenia) represents a unique and mechanistically proven severe complication, which differs significantly from the hypothetical mechanisms proposed for other occasional immune-mediated events. As Figure 2. illustrates, these mechanisms demonstrate marked differences in causality and strength of supporting evidence.

4.8. A. Innate Immune Activation and Reactogenicity

Mechanism Description: Common and transient GI symptoms can be attributed to systemic cytokine illustrates, by vaccination, reflecting expected host innate immune activation. Upon entering cells, mRNA or adenoviral vectors activate pattern recognition receptors (PRRs), leading to the release of pro-inflammatory cytokines (e.g., IL-6, TNF-α). These cytokines may exert effects on GI motility, the chemoreceptor trigger zone (CTZ) in the central nervous system, or directly on the enteric nervous system, resulting in symptoms such as nausea, vomiting, and diarrhea [1,2,9,11].

4.9. B. Immune-Mediated Mechanisms / Molecular Mimicry

Mechanism Description: For occasional autoimmune phenomena (e.g., AIH-like cases), the primary hypotheses involve molecular mimicry or non-specific immune activation. Vaccine components or antigens may share structural similarities with host autoantigens in GI tissues, thereby triggering cross-reactive immune attacks on GI organs [18,7,14].

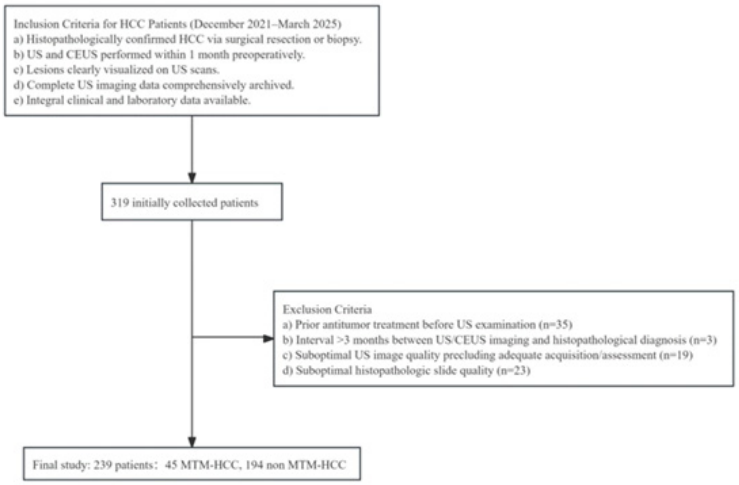

Figure 1: Flow diagram for patient enrollment in this study. US: conventional ultrasound; CEUS: contrast-enhanced ultrasound; HCC: hepatocellular carcinoma; MTM-HCC: thick trabecular-mass type hepatocellular carcinoma.

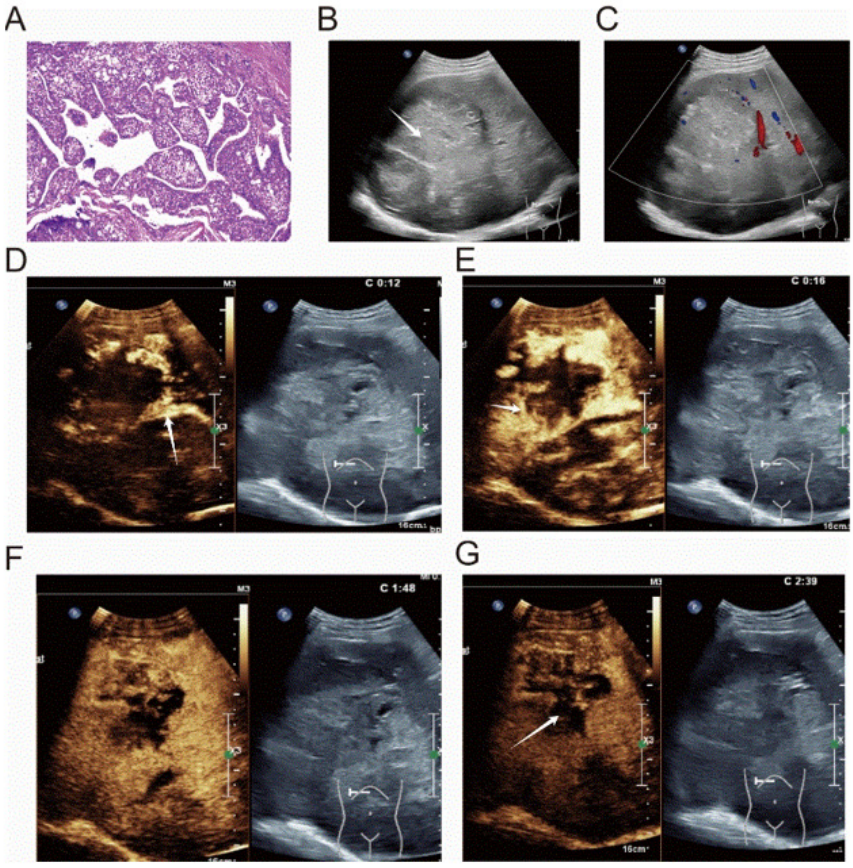

Figure 2: Diagnostic images for a 60-year-old male with hepatitis B virus-related cirrhosis and macro trabecular-massive hepatocellular carcinoma (MTM-HCC). Laboratory data showed an AFP level of 1210 ng/mL, AST 65 U/L, and neutrophil-to-lymphocyte ratio (NLR) > 6. Pathological immunohistochemistry demonstrated a Ki-67 index of 60% (A). Micrograph reveals a macro trabecular-massive growth pattern (B). Two-dimensional ultrasound image demonstrates an approximately 8.7-cm HCC in segment VIII of the right hepatic lobe. The mass exhibits heterogeneous echogenicity, a peripheral hypoechoic halo, and a "nodule-in-nodule" appearance. The lesion is indicated by white arrows (C). Peripheral rim-like blood flow signals are observed around the mass. (D)–(G): Preoperative contrast-enhanced US (CEUS) images. (D), (E): In the arterial phase, the lesion shows peripheral nodular hyperenhancement. Intratumorally arteries (D) and peritumoral arteries (E) are visible, each marked by white arrows (F). In the portal venous phase, the lesion exhibits marked washout, appearing hypoechoic. 9G) In the delayed phase, the lesion shows sustained hypo-enhancement. Non-enhancing necrotic areas are present throughout all phases. According to the CEUS Liver Imaging Reporting and Data System (CEUS LI-RADS) 2017, this nodule was classified as LR-M.

Table 1: Clinical and Histopathological Characteristics of Patients Between the Two Groups.

Characteristic	Non-MTM-HCC(n = 194)	MTM-HCC (n = 45)	P
Sex, n(%)			0.751
Female	43 (22.16)	9 (20.00)	
male	151 (77.84)	36 (80.00)	
age/Year	57.60 ± 9.37	55.91 ± 10.57	0.288
AFP（ng/mL）	32.55 (4.29, 261.60)	1210.00 (475.00, 1210.00)	<.001
CA199(U/mL)	18.25 (9.19, 38.82)	23.90 (12.70, 45.10)	0.304
ALT(U/L)	41.00 (25.25, 114.75)	49.00 (33.00, 151.00)	0.152
AST(U/L)	56.50 (37.00, 140.50)	100.00 (53.00, 215.00)	0.005
ALB(g/L)	36.00 (31.90, 40.10)	36.70 (34.00, 38.10)	0.955
TBIL（μmol/l）	22.75 (16.15, 33.70)	25.40 (19.20, 34.50)	0.437
Hb(g/L)	143.00 (124.00, 156.50)	144.00 (119.00, 154.00)	0.828
PLT（×10^9/l）	132.00 (88.25, 190.00)	152.00 (112.00, 192.00)	0.105
N（×10^9/l）	4.16 (2.31, 6.72)	5.24 (3.49, 7.36)	0.045
L（×10^9/l）	1.03 (0.70, 1.50)	0.84 (0.66, 1.32)	0.078
NLR	3.62 (2.16, 8.03)	5.19 (3.31, 14.00)	0.009
HBV, n (%)			0.677
No	46 (23.71)	12 (26.67)	
Yes	148 (76.29)	33 (73.33)	
liver cirrhosis, n(%)			
No	49 (25.26)	11 (24.44)	
Yes	145 (74.74)	34 (75.56)	
CD34, n (%)			
	16 (8.25)	2 (4.44)	
	178 (91.75)	43 (95.56)	
Glypican3, n (%)			0.329
	38 (19.59)	6 (13.33)	
	156 (80.41)	39 (86.67)	
CK19, n (%)			0.014
-	161 (82.99)	30 (66.67)	
+	33 (17.01)	15 (33.33)	
Edmonson-Steiner Grade (I-II/III-IV, n (%)			<.001
I-II	172 (88.66)	30 (66.67)	
III-IV	22 (11.34)	15 (33.33)	
Ki67(%)	30.00 (20.00, 40.00)	40.00 (30.00, 60.00)	<.001

Unless otherwise specified, data are presented as median with interquartile range in parentheses.

Abbreviations: MTM (thick trabecular-mass type), HCC (hepatocellular carcinoma), AFP (alpha-fetoprotein), CA199 (carbohydrate antigen 199), ALT (alanine aminotransferase), AST (aspartate aminotransferase), ALB (albumin), TBIL (total bilirubin), Hb (hemoglobin), PLT (platelet), N (neutrophil), L (lymphocyte), NLR (neutrophil/lymphocyte ratio), HBV (hepatitis B virus).

a. Data are presented as mean ± standard deviation. b. Data are presented as number of patients; data in parentheses are percentages.

Table 2: Comparison Results of US and CEUS Features Between the Two Groups of Patients.

Characteristics	Non-MTM-HCC (n = 194)	MTM-HCC (n = 45)	P
Number of tumors, n (%)			0.133
Isolated	93 (47.94)	16 (35.56)	
Multiple	101 (52.06)	29 (64.44)	
Echo, n(%)			0.599
Hypoechoic	124 (63.92)	31 (68.89)	
isoechoic	9 (4.64)	1 (2.22)	
Mixed echo	15 (7.73)	1 (2.22)	
Hyperechoic	46 (23.71)	12 (26.67)	
Maximum diameter（cm）	3.70 (2.20, 5.47)	6.60 (3.80, 8.20)	<.001
Size classification, n (%)			<.001
＜3cm	73 (37.63)	7 (15.56)	
2.3-5cm	61 (31.44)	8 (17.78)	
＞5cm	60 (30.93)	30 (66.67)	
Echo homogeneity, n (%)			0.003
Uniform	53 (27.32)	3 (6.67)	
Non-uniform	141 (72.68)	42 (93.33)	
CDFI, n (%)			0.093
Grade 0	41 (21.13)	5 (11.11)	
Grade I	62 (31.96)	10 (22.22)	
Grade II	6 (3.09)	1 (2.22)	
Grade III	85 (43.81)	29 (64.44)	
Morphology, n (%)			0.267
Regular	149 (76.80)	31 (68.89)	
Irregular	45 (23.20)	14 (31.11)	
Tumor margin, n (%)			<.001
Clear	111 (57.22)	11 (24.44)	
Indistinct	83 (42.78)	34 (75.56)	
Encapsulation, n (%)			0.070
Yes	98 (50.52)	16 (35.56)	
No	96 (49.48)	29 (64.44)	
Knot within a knot, n (%)			0.006
Yes	81 (41.75)	29 (64.44)	
No	113 (58.25)	16 (35.56)	
AP Start Enhancement Time（s）	15.00 (13.00, 18.00)	15.00 (14.00, 17.00)	0.820
Whether Range Expanded After Enhancement, n (%)			0.045
Yes	37 (19.07)	3 (6.67)	
No	157 (80.93)	42 (93.33)	
AP Enhancement Pattern, n (%)			0.777
High Enhancement	171 (88.14)	42 (93.33)	
Isotopic Enhancement	20 (10.31)	3 (6.67)	
Low Enhancement	3 (1.55)	0 (0.00)	
Arterial Phase Enhancement Pattern, n (%)			<.001
Synchronous Enhancement	116 (59.79)	8 (17.78)	

Peripheral Nodular Enhancement	49 (25.26)	31 (68.89)	
Annular Enhancement	11 (5.67)	2 (4.44)	
Centrifugal Enhancement	18 (9.28)	4 (8.89)	
Start of Decay Time, n (%)			0.226
Ultra-Early Decay（＜30）	8 (4.12)	4 (8.89)	
Early Decay（＜60s）	68 (35.05)	20 (44.44)	
Late Decay（＞60s）	118 (60.83)	21 (46.67)	
H-PVP Decay Degree, n(%)			0.027
No Decay	56 (28.87)	5 (11.11)	
Mild Decay	78 (40.21)	19 (42.22)	
Marked Decay	60 (30.93)	21 (46.67)	
DP Clearance Degree, n(%)			0.127
No Clearance	28 (14.43)	2 (4.44)	
Incomplete Clearance	88 (45.36)	18 (40.00)	
Complete Clearance	78 (40.21)	25 (55.56)	
No enhancement in necrotic areas, n (%)			<.001
No	148 (76.29)	15 (33.33)	
Yes	46 (23.71)	30 (66.67)	
Intranodular artery, n (%)			<.001
No	149 (76.80)	12 (26.67)	
Yes	45 (23.20)	33 (73.33)	
FA, n (%)			0.001
No	124 (63.92)	17 (37.78)	
Yes	70 (36.08)	28 (62.22)	
VTT, n (%)			<.001
No	155 (79.90)	24 (53.33)	
Yes	39 (20.10)	21 (46.67)	
LI-RADS, n (%)			0.746
3	5 (3.38)	0 (0.00)	
4	30 (20.27)	5 (15.15)	
5	99 (66.89)	24 (72.73)	
M	14 (9.46)	4 (12.12)	

Table 3.1: Analysis of Predictors in Binary Logistic Regression for MTM-HCC.

Variable	P-value of univariate analysis	P-value of multivariate analysis	Multivariate OR (95%CI)
AFP≥467ng/mL	<.001	<.001	1.01 (1.01 ~ 1.01)
AST	0.575	0.334	1.00 (1.00 ~ 1.00)
N	0.656	0.509	0.97 (0.88 ~ 1.07)
NLR	0.128	0.054	1.06 (1.00 ~ 1.13)
Maximum tumor diameter	<.001	0.529	0.93 (0.74 ~ 1.17)
Tumor size classification	<.001	0.528	0.72 (0.27 ~ 1.97)
Echogenicity homogeneity	0.007	0.191	3.20 (0.56 ~ 18.29)
Tumor margins	<.001	0.392	1.60 (0.54 ~ 4.71)
Double-peaked enhancement pattern	0.007	0.513	0.71 (0.26 ~ 1.97)

Enhanced area	0.056	0.178	3.09 (0.60 ~ 15.91)
Arterial phase enhancement pattern	0.011	0.684	0.90 (0.53 ~ 1.51)
Degree of H-PVP washout	0.009	0.896	0.95 (0.43 ~ 2.09)
Necrotic areas without enhancement	<.001	0.003	5.92 (1.82 ~ 19.30)
Intramural arteries	<.001	<.001	6.61 (2.28 ~ 19.22)
FA	0.002	0.025	3.13 (1.15 ~ 8.50)
VTT	<.001	0.961	1.03 (0.31 ~ 3.41)

Note: Data in parentheses are 95% confidence intervals.
Abbreviations: MTM (thick trabecular-mass type), HCC (hepatocellular carcinoma), AFP (alpha-fetoprotein), AST (aspartate aminotransferase), NLR (neutrophil/lymphocyte ratio), AP (arterial phase), H-PVP (portal venous phase < 60s), FA (peritumoral feeding artery), VTT (venous tumour thrombus), OR (odds ratio), CI (confidence interval).

Table 3.2: Confusion Matrix.

AUC (95%CI)	Accuracy (95%CI)	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)	cutoff
0.915 (0.860-0.970)	0.879 (0.830-0.917)	0.887 (0.842 - 0.931)	0.844 (0.739 - 0.950)	0.961 (0.932 - 0.989)	0.633 (0.511 - 0.755)	0.255

Note: AUC (Area Under the Curve), Accuracy (accuracy), Sensitivity (sensitivity), Specificity (specificity), PPV (Positive Predictive Value), NPV (Negative Predictive Value), cut-off (critical value).

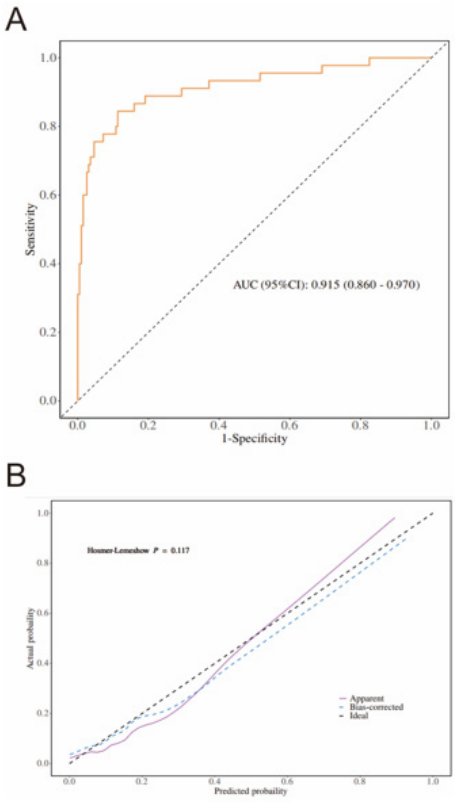

Figure 3: Performance evaluation of the predictive model for macro trabecular-massive hepatocellular carcinoma (MTM-HCC). (A) Receiver operating characteristic (ROC) curve illustrating the model's discriminatory ability, with an area under the curve (AUC) of 0.915 (95% confidence interval [CI]: 0.860–0.970). (B) Calibration plot showing the agreement between predicted and actual probabilities. The black dashed line represents ideal prediction. The Hosmer-Lem show test yields a P-value of 0.117, indicating good calibration of the model.

4.10. C. The Specific Mechanism of VITT: Anti-PF4 Antibodies

Mechanism Description: The occurrence of VITT possesses a unique and established biological plausibility. Following adenoviral vector vaccine administration, it induces the production of platelet-activating anti-platelet factor 4 (anti-PF4) antibodies. These antibodies bind to PF4 complexes, leading to intense platelet activation and aggregation, culminating in a syndrome resembling Heparin-Induced Thrombocytopenia (HIT).

Clinical Manifestation Link: This pathological process results in thrombosis in unusual vascular beds, including the splanchnic veins supplying the intestines, thereby explaining VITT-related acute abdominal symptoms.

Strength of Evidence: This mechanism has garnered robust clinical and laboratory supported by NEJM and other series [2, 6,27].

5. Causality Assessment & Epidemiology

Causality for common mild GI AEs is straightforward (temporal and biologically plausible). For severe and specific GI conditions, causality assessment should use Bradford Hill principles: temporality, strength of association (epidemiologic risk ratios), consistency across studies, biological gradient, plausibility, and exclusion of alternative causes [2,3,9,11]. For most severe GI events (AIH, appendicitis, pancreatitis), population studies to date have not shown clear, consistent increases attributable to vaccination, and many published cases remain temporally associated but unproven as vaccine caused. VITT with splanchnic thrombosis is an important exception where mechanistic and epidemiologic evidence links the adenoviral-vector vaccines to the syndrome [6,7,27,29].

6. Clinical Approach and Guidance

Mild symptoms require supportive care. Severe abdominal/neurologic symptoms and abnormal liver function need standard workup and treatment. All serious AEs must be reported for safety monitoring.

A. Mild GI symptoms: symptomatic care (oral fluids, antiemetics, antidiarrheals if needed), reassurance [2,3,7,9].

B. Severe or persistent abdominal pain, GI bleeding, persistent high fevers, or neurologic symptoms within 4-28 days after adenoviral-vector vaccination: consider urgent evaluation for VITT and splanchnic thrombosis (CBC, D-dimer, platelet factor 4 antibody tests, imaging). Avoid empiric heparin until VITT is considered [2,6,23,24,27].

C. New abnormal liver tests after vaccination: perform standard hepatitis workup (viral serologies, autoimmune markers, medication review) and consider hepatology referral if severe; treat AIH-like presentations per standard protocols when diagnosis supported [2,6,7,9,17].

D. Report suspected serious or unexpected AEs to local pharmacovigilance systems (VAERS, EudraVigilance, national equivalents) to support ongoing safety monitoring.

7. Risk–Benefit Perspective

Even where rare GI-related serious events have been reported, the absolute risk is very small compared with the benefits of COVID-19 vaccination in preventing severe COVID-19, hospitalization, and death. Where specific vaccine types have higher risk profiles for rare events (e.g., VITT after certain adenoviral vaccines), many countries adjusted recommendations (age stratification, alternative platforms). Communication should emphasize the rarity of serious GI complications, the self-limited nature of common GI symptoms, and the protective public-health value of vaccination [10,11,16,17].

9. Gaps and Research Needs

Despite growing real-world evidence, the absolute risks of gastrointestinal (GI) and related complications following COVID-19 vaccination remain insufficiently defined. Key knowledge gaps particularly for rare adverse events, highlight the need for coordinated efforts encompassing large-scale epidemiological studies, mechanistic research on host susceptibility, and standardized reporting systems. Strengthening these domains will enable more accurate risk estimates, improve causal assessment, and enhance global pharmacovigilance.

A. High-quality, population-based studies with active surveillance to quantify absolute risks of rare GI events across vaccine platforms [7,14,19,22].

B. Mechanistic research to identify host susceptibility markers for autoimmune-like or thrombotic complications [2,9,11].

C. Continued harmonized reporting and pooled analyses to increase power to detect or refute rare associations [1,2,9,11].

9. Conclusion

Most GI manifestations after COVID-19 vaccination are mild, transient, and consistent with expected reactogenicity. Rare but clinically important events most notably VITT with splanchnic thrombosis after adenoviral-vector vaccines have clear mechanistic and epidemiologic evidence and require early recognition [2,6,27-29]. For other conditions reported in case series (AIH, appendicitis, pancreatitis, acute abdomen), causality remains uncertain at the population level; clinicians should evaluate symptoms normally, investigate alarm features aggressively, and report suspected vaccine-related events to surveillance systems. Overall, vaccine benefits substantially outweigh the small risks of serious GI complications [1,10,11,9].

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