

Liver Function Abnormalities and Hepatic Enzyme Profiles in Patients with Nasopharyngeal Carcinoma: A Review

Zahraa Ali Mohammed ¹, Ali Hussein Jameel ^{2,*} and Nahid Sabah Aldin Saber ³

1,2,3 Department of Clinical Laboratory Sciences, College of Pharmacy, University of Al-Qadisiyah, Diwaniyah, Iraq.

Received 10th April 2026,
Accepted 10th June 2026

Cite this: NJBM. 2026, 2(1), 22-30

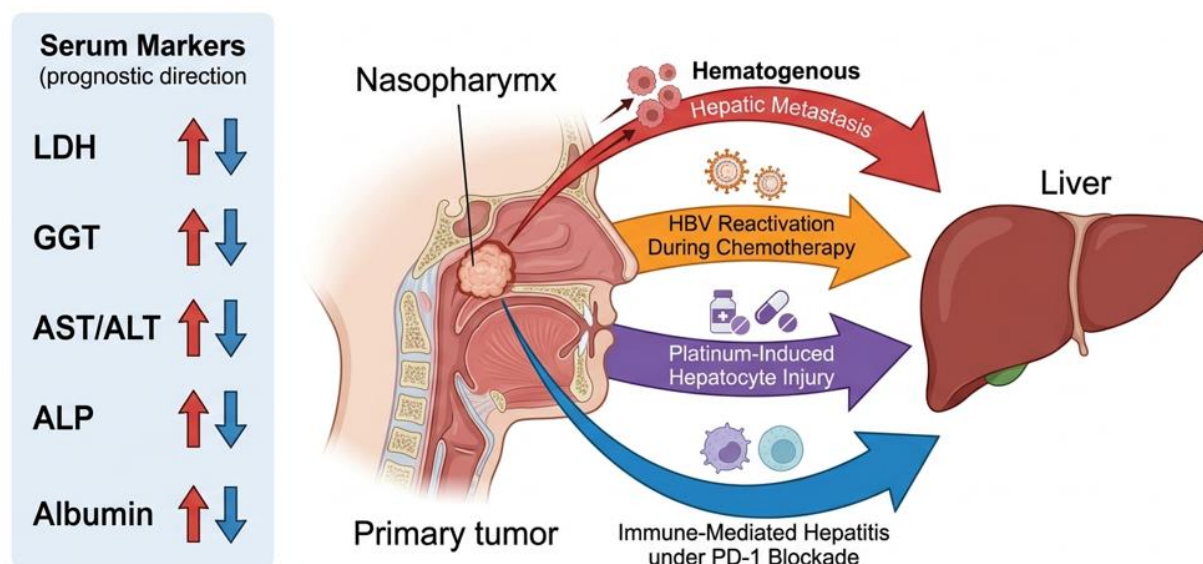
Keywords: Nasopharyngeal carcinoma; Liver function tests; Hepatic enzymes; Lactate dehydrogenase; Gamma-glutamyl transferase; De Ritis ratio; Hepatitis B reactivation; Hepatotoxicity; Prognosis

ABSTRACT. Nasopharyngeal carcinoma (NPC) is an epithelial malignancy associated with Epstein-Barr virus which is characterised by a high degree of geographic clustering in Southern China, Southeast Asia and some areas of North Africa and the Middle East. The clinical presentation is dominated by the nasopharynx and its draining lymphatics but the liver is recurrently involved in the natural history and therapy of the disease and aberrant hepatic biochemistry is seen significantly more frequently than is typically acknowledged. This study brings together the scattered data of liver function impairments and hepatic enzyme profile in NPC and attempts to interpret the reasons for their occurrence and the significance. We discuss four major pathways in which the liver is involved: synchronous or metachronous hepatic metastasis, reactivation of chronic hepatitis B virus in the setting of cytotoxic therapy, drug-induced hepatotoxicity from platinum-based regimens and, more recently, immune-related hepatitis due to PD-1 blockade. We then review the literature on the use of individual liver-derived markers as prognostic tools, with particular emphasis on lactate dehydrogenase, gamma-glutamyl transferase, the aspartate-to-alanine aminotransferase (De Ritis) ratio, alkaline phosphatase and composite indices such as the albumin-to-alkaline-phosphatase ratio. A common feature across the research is that inexpensive, frequently available biochemical assays have significant predictive information that is, at least in part, independent of TNM stage. We end with practical implications for baseline screening, antiviral prophylaxis and on-treatment surveillance and flag the methodological weaknesses of retrospective design, inconsistent cut-offs and limited geographic diversity that still limit confident clinical translation.

HIGHLIGHTS

- Hepatic dysfunction in NPC arises from at least four separate mechanisms: liver metastasis, HBV reactivation, chemotherapy-induced injury, and immune-checkpoint-inhibitor hepatitis.
- The liver is among the three most frequent sites of distant failure, and hepatic involvement carries a notably worse outcome than other metastatic patterns.
- Pretreatment serum LDH is the most consistently validated liver-related prognostic marker, predicting distant metastasis and shorter overall survival.
- GGT, the De Ritis ratio, alkaline phosphatase, and the albumin-to-alkaline-phosphatase ratio add independent prognostic value beyond conventional staging.
- HBV screening and antiviral prophylaxis are essential in endemic settings, where reactivation can interrupt treatment and occasionally prove fatal.

GRAPHICAL ABSTRACT



1. INTRODUCTION

Nasopharyngeal cancer has a unique place in head and neck oncology. Its epidemiology is strongly regional, its biology is linked to the Epstein-Barr virus (EBV), and unlike most squamous tumours of the upper aerodigestive tract it is exquisitely radiosensitive and chemosensitive, so that radiotherapy with concurrent or induction chemotherapy forms the backbone of curative treatment [1,2]. The disease is endemic in southern China and Southeast Asia with minor foci throughout North Africa and the Arab world. The association with EBV is increasingly used therapeutically, both for screening through plasma viral DNA and for risk stratification during follow-up [3,4]. The use of platinum doublets remains the standard of care in locoregionally advanced or recurrent and metastatic disease and the addition of anti-PD-1 antibodies to first-line treatment of recurrent or metastatic NPC has been added in the past few years [5,6,7].

In this context, the liver often gets relatively little attention, yet it intersects with NPC at practically every point of the patient journey. It is a common location of distant dissemination; the organ most damaged by the cytotoxic medications used to treat the cancer; and, in areas where chronic hepatitis B is common, the source of a treatment-limiting and sometimes deadly consequence. Alongside these mechanistic linkages, a separate and generally parallel body of literature has accumulated in which liver-derived enzymes, tested at baseline as part of regular biochemistry, are regarded as prognostic biomarkers in their own right. This review seeks to bring these strands together, to describe the mechanisms that perturb hepatic biochemistry in NPC, to summarise the data for individual enzymes as prognostic indicators and to consider how this information may be used at the bedside.

2. NASOPHARYNGEAL CARCINOMA: A BRIEF CLINICAL AND EPIDEMIOLOGICAL CONTEXT

A brief orientation before turning to the liver is useful. The NPC originates from the epithelium lining the nasopharynx, most commonly in the fossa of Rosenmüller. The World Health Organization defines keratinising, non-keratinising differentiated and non-keratinising undifferentiated variants. In endemic populations the undifferentiated type predominates and is almost uniformly EBV-positive while the keratinising variant is significantly more common in low-incidence locations [1,2]. Both the high rate of nodal disease at diagnosis and the large risk of distant failure despite great locoregional control with current intensity-modulated radiation are explained by late presentation and abundant submucosal lymphatic supply of the tumour.

Plasma EBV DNA has appeared as a clinically relevant marker in this scenario. A consistently detectable concentration following radiation is one of the strongest indicators of relapse and death and repeated measurement currently guides surveillance in many centres [3]. The same mechanism underlies population screening efforts using circulating EBV DNA to detect early, asymptomatic illness [4]. These methods are relevant to the present topic because hepatic events, whether metastatic or treatment-related, often occur simultaneously with, and occasionally preceded by, changes in viral load and in the regular biochemistry obtained at the same clinic visits. Thus, to understand hepatic anomalies in NPC, liver chemistry should not be interpreted in isolation but rather in the context of staging, viral, and therapeutic factors that influence its production.

Table 1. Histological subtypes of nasopharyngeal cancer (World Health Organization) and their typical connection with Epstein–Barr virus and regional distribution.

WHO histological subtype	Typical EBV association	Geographic / epidemiological distribution
Keratinizing squamous cell carcinoma (WHO type I)	Inconsistent / weak; not reliably EBV-associated	Relatively more common in low-incidence (non-endemic) regions
Non-keratinizing differentiated carcinoma (WHO type II)	EBV-associated	Intermediate; encountered across both endemic and non-endemic areas
Non-keratinizing undifferentiated carcinoma (WHO type III)	Almost universally EBV-positive	Predominant subtype in endemic populations (Southern China, Southeast Asia)

EBV, Epstein–Barr virus; WHO, World Health Organization. Histological classification and its association with EBV and geography are based on refs [1,2].

3. WHAT LIVER FUNCTION TESTS AND HEPATIC ENZYMES ACTUALLY MEASURE

Much of the predictive literature is based on a few serum tests so it is worth briefly restating what each of these reflects, as the interpretation in cancer patients is not necessarily the same as in general hepatology. Aminotransferases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) are intracellular enzymes that are released in the setting of hepatocyte injury. ALT is relatively liver specific, whereas AST is also found in muscle, myocardium, and erythrocytes, so an elevation in AST is less specific for the liver. Alkaline phosphatase (ALP) and gamma glutamyl transferase (GGT) are often considered together as cholestatic or canalicular markers. Both have important extrahepatic sources. ALP is highly expressed in bone and increases with osteoblastic activity. GGT is a membrane bound enzyme involved in glutathione metabolism, is induced in many tissues and is influenced by alcohol and enzyme inducing drugs. Serum bilirubin indicates

the balance between haem turnover and hepatic conjugation and excretion, and albumin measures hepatic synthetic ability, which is lowered concurrently by inflammation and starvation. Finally, lactate dehydrogenase (LDH) is not a liver function test in the strict sense, but a glycolytic enzyme found in virtually all tissues, and its elevation in cancer is generally interpreted as a signature of tumour burden, hypoxia and Warburg-type metabolism of proliferating malignant cells, rather than evidence of liver disease [15].

That difference is important. In NPC several of these so-called liver markers carry prognostic weight precisely because they are not reporting on the liver: ALP often rises because of bone metastasis, GGT and LDH track tumour metabolism and aggressiveness, and the De Ritis ratio appears to capture a metabolic phenotype rather than hepatocellular damage. The reviewer or clinician therefore has to hold two questions in mind at once, namely whether the abnormality is telling them about the liver or about the cancer, and the answer is frequently the latter.

Table 2. Principal hepatic biochemical markers, their major tissue sources, and their interpretation in the oncology setting.

Marker	Major tissue source(s)	Interpretation in the oncology / NPC setting
ALT (alanine aminotransferase)	Hepatocytes (relatively liver-specific)	Released on hepatocellular injury; rises with drug-induced toxicity and immune-related hepatitis; component of the AST/ALT (De Ritis) ratio
AST (aspartate aminotransferase)	Hepatocytes, plus skeletal muscle, myocardium and erythrocytes (less liver-specific)	Hepatocellular injury; combined with ALT as the De Ritis ratio, which reflects a metabolic phenotype rather than pure hepatocyte damage
ALP (alkaline phosphatase)	Liver (canalicular) and bone (osteoblasts)	Cholestatic/canalicular marker, but in NPC frequently elevated by osteoblastic bone metastasis rather than by the liver; denominator of the AAPR
GGT (gamma-glutamyl transferase)	Hepatobiliary epithelium; widely induced in many tissues; affected by alcohol and enzyme-inducing drugs	Canalicular marker; in NPC tracks tumour redox balance, drug resistance and aggressiveness more than simple cholestasis
Total bilirubin	Product of haem catabolism; cleared by hepatic conjugation and excretion	Reflects the balance of haem turnover against hepatic excretory capacity; hyperbilirubinaemia signals advanced cholestasis or extensive hepatic metastasis
Albumin	Synthesized by the liver	Marker of hepatic synthetic capacity; also depressed by systemic inflammation and malnutrition/cachexia; numerator of the AAPR
LDH (lactate dehydrogenase)	Ubiquitous (present in virtually all tissues)	Not a true liver function test; a glycolytic enzyme read as a signature of tumour burden, hypoxia and Warburg-type metabolism; the strongest single prognostic marker in NPC

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; LDH, lactate dehydrogenase; AAPR, albumin-to-alkaline-phosphatase ratio; NPC, nasopharyngeal carcinoma.

4. MECHANISMS OF HEPATIC INVOLVEMENT IN NASOPHARYNGEAL CARCINOMA

Hepatic abnormalities in NPC do not have a single cause, and conflating them is a frequent source of confusion in the literature. At least four mechanisms operate, sometimes simultaneously in the same patient, and each leaves a somewhat different biochemical and clinical fingerprint.

4.1 Hepatic metastasis

Distant metastasis is the major cause of treatment failure in NPC, and the liver is always one of the most commonly involved organs. In a major SEER-based investigation of metastatic NPC, the liver was the most common location of dissemination aside from bone, along with the lung, and significantly, the presence of liver metastasis was related with worse cancer-specific survival independent of the number of other organs involved [8]. Such singling-out of liver disease as a specially unfavourable pattern is repeated in series. In a retrospective study of patients with synchronous liver metastasis, median survival was approximately nineteen months with aggressive systemic therapy, and elevated serum LDH (>~245 IU/L) as well as poor performance status and a poor chemotherapy response were independent predictors of poorer survival [9]. Biochemically, established hepatic metastases often provide a cholestatic or mixed picture with elevated ALP and GGT and in advanced instances hyperbilirubinaemia; transaminases may be only moderately raised until parenchymal replacement is substantial. Such alterations may be minor and nonspecific early on, and therefore easily attributed to treatment rather than progression. This is one practical reason to evaluate on-treatment liver chemistry carefully, together with imaging and EBV DNA.

4.2 Reactivation of chronic hepatitis B virus

In endemic NPC countries, chronic hepatitis B virus (HBV) infection is prevalent in the population, with as many as one in ten people in some parts of Asia being infected. This means a significant minority of patients present with the virus prior to commencing chemotherapy. Cytotoxic treatment impairs host immune regulation of HBV with a rise in viral replication and subsequent hepatocyte clearance when immune function is restored, which presents as a hepatic flare. The clinical spectrum includes asymptomatic elevation of transaminases to fulminant hepatic failure and even modest occurrences are detrimental since they break or limit anticancer treatment [10]. The risk variables discovered across cancer populations are quantifiable baseline HBV DNA level and use of corticosteroids, and the condition is validated by a hepatic pattern of liver enzymes with measurable elevation in blood HBV DNA [10]. The reported benefit of antiviral prophylaxis supports the practical importance of this mechanism. In NPC patients, prophylactic lamivudine significantly reduced the incidence of HBV reactivation and chemotherapy interruption compared with historical controls [11]. A more comprehensive systematic review and meta-analysis of solid-tumour chemotherapy demonstrated that antiviral prophylaxis reduces the likelihood

of reactivation and supports regular screening of patients with chronic or resolved infection prior to cytotoxic therapy [12]. Thus, for the clinician faced with aberrant liver chemistry following medication in an endemic situation, HBV reactivation is a diagnosis to be aggressively excluded, not one to be assumed away.

4.3 Chemotherapy-induced hepatotoxicity

Platinum-based regimens, which are themselves hepatotoxic, form the backbone of NPC treatment. Specifically, cisplatin accumulates in hepatocytes and leads to injury via overproduction of reactive oxygen species, depletion of reduced glutathione, lipid peroxidation and activation of the apoptotic pathways. Histological evidence of disrupted hepatic architecture in experimental models has been described [13]. Clinically this tends to manifest as a hepatocellular pattern of enzyme increase, generally dose related and often temporary while higher cumulative exposure can result in a more persistent derangement. Gemcitabine and 5-fluorouracil, the standard partners for cisplatin in recurrent and metastatic illness, contribute additional, generally milder, hepatic effects [5]. The key clinical issue is one of attribution: an ALT/AST rise mid-treatment could be due to drug toxicity, HBV re-activation or progressive metastatic disease, and the ability to distinguish between these possibilities rather than reflexively dose-reducing has clear implications for both safety and oncologic outcome.

4.4 Immune-checkpoint-inhibitor-related hepatitis

The incorporation of anti-PD-1 antibodies into first-line treatment of recurrent and metastatic NPC has introduced a further, immunologically distinct cause of liver injury [6,7]. Immune-mediated hepatitis is a recognised immune-related adverse event of checkpoint blockade; it is typically a hepatocellular or mixed transaminitis, can occur weeks to months after initiation, and, unlike most chemotherapy toxicity, is managed with corticosteroids and immunosuppression rather than simple drug interruption. Although often manageable, immune hepatitis accounts for a disproportionate share of fatal immune-related events, so vigilance is warranted as these agents become routine. It is against this evolving therapeutic landscape that baseline and on-treatment liver function indicators have acquired renewed prognostic interest; indeed, a recent nomogram built from pretreatment liver function tests, incorporating ALT, the AST/ALT ratio, and LDH, predicted progression-free survival in NPC patients receiving PD-1 inhibitor therapy more accurately than TNM stage alone [14].

4.5 A note on radiotherapy

For completeness, it is worth stating what does not usually happen. In contrast to abdominal or hepatobiliary malignancies, the radiotherapy fields used for NPC do not encompass the liver, so classic radiation-induced liver disease is not a meaningful contributor to hepatic abnormality in this population. When liver chemistry deteriorates during or after radiotherapy for NPC, the explanation lies in one of the mechanisms above, namely metastasis, viral reactivation, or systemic-therapy toxicity, rather than in hepatic irradiation.

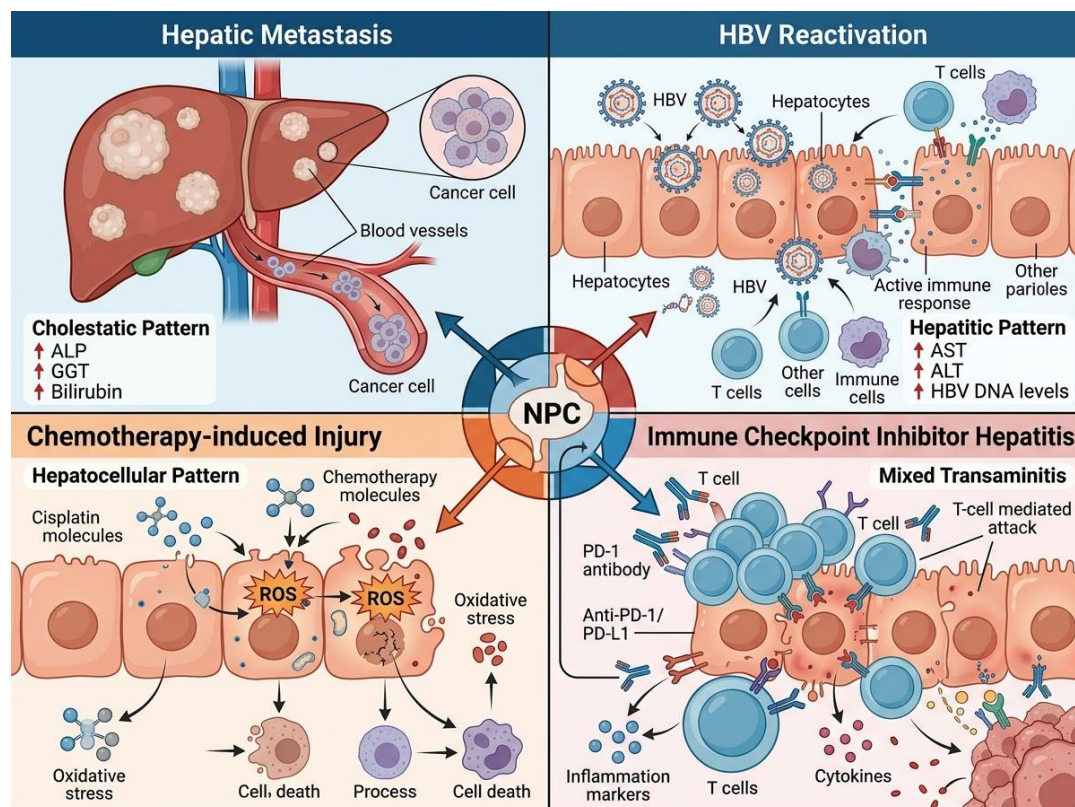


Figure 1. Illustrated summary of the principal mechanisms linking nasopharyngeal carcinoma and its treatment to liver function abnormalities (hepatic metastasis, HBV reactivation, chemotherapy-induced injury, and immune-checkpoint-inhibitor hepatitis), with the corresponding biochemical pattern annotated for each.

5. HEPATIC ENZYMES AS PROGNOSTIC BIOMARKERS

If the mechanistic story explains why liver chemistry is disturbed, a separate and arguably larger literature asks a different question: does that chemistry, measured before treatment, predict outcome? The short answer is that several markers do, often independently of stage, and the recurring appeal is that they are inexpensive and universally available.

5.1 Lactate dehydrogenase

Of them, LDH is the most researched marker in NPC, and the evidence is relatively consistent. Study after study has shown that increased pretreatment LDH, a glycolytic enzyme and marker of cancer metabolism and hypoxia, is associated with increased metastatic potential and poorer survival. A meta-analysis in Chinese NPC population demonstrated that increased pretreatment LDH was substantially linked with worse overall survival, distant-metastasis-free survival and disease-free survival, which supported its use as a prognostic factor [15]. In addition to the static baseline value, the trajectory of LDH seems informative; in patients treated with radical intensity-modulated radiotherapy, both elevated pre- and post-treatment LDH predicted distant metastasis and poorer overall survival, prompting the authors to advocate routine measurement before and after radiotherapy [16]. The marker has also survived the immunotherapy period when pre-treatment LDH in combination with the number of metastatic sites was useful to separate individuals more or less likely to benefit from anti-PD-1 therapy [17]. Various cut-offs were

employed in different investigations, with values in the range of roughly 200 to 250 IU/L recurring, and this heterogeneity is a genuine limitation, but the direction of effect is unusually stable.

5.2 Gamma-glutamyl transferase

The interest in GGT has been driven by its role in glutathione metabolism, which has molecular links to tumour redox balance, drug resistance and proliferation, rather than solely to cholestasis. Two independent NPC cohorts reported that high pretreatment serum GGT predicted inferior outcome. In one series of 222 patients, those in the high-GGT group had markedly worse three-year overall, progression-free, locoregional-relapse-free, and distant-metastasis-free survival than the low-GGT group, and notably the GGT level was not simply a surrogate for T stage, N stage, or overall TNM stage [18]. A second study of 374 patients identified a cut-off around 23 U/L and found elevated GGT to be an independent predictor of shorter local-recurrence-free, progression-free, and overall survival on multivariate analysis [19]. The fact that two groups, using different cut-offs and populations, reached convergent conclusions strengthens the case that GGT carries information about tumour aggressiveness in NPC.

5.3 The De Ritis ratio and the transaminases

The AST/ALT (De Ritis) ratio is an old hepatology index that has been repurposed as a cancer biomarker, on the reasoning that the relative activities of the two aminotransferases reflect shifts in cellular energy metabolism characteristic of malignancy. In nonmetastatic NPC, a high pretreatment De Ritis ratio was reported to predict poorer prognosis [20], a finding consistent

with the same ratio's prognostic value in other head and neck sites, such as oral and oropharyngeal squamous cell carcinoma, where an AST/ALT ratio above approximately 1.44 was independently associated with worse cancer-specific and overall survival [21]. The ratio has additionally been linked to radiosensitivity: in head and neck carcinoma patients, the De Ritis ratio predicted local disease control after radiotherapy [22]. Whether the ratio adds much beyond LDH and GGT in NPC specifically remains to be clarified, but its near-zero cost makes it an attractive candidate for incorporation into composite models such as the PD-1 nomogram discussed earlier [14].

5.4 Alkaline phosphatase and the albumin-to-alkaline-phosphatase ratio

ALP is a particularly instructive marker because its prognostic value in NPC is bound up with its dual origin. Elevated pretreatment serum ALP has been associated with more advanced T classification and stage and with poorer overall and tumour-free survival in a large NPC cohort, and analyses pairing ALP with LDH found that increased levels of both at baseline behaved as poor prognostic factors [23,24]. Much of ALP's signal in NPC, however, reflects bone rather than liver, since osteoblastic skeletal metastasis, the single most common metastatic pattern in this disease, drives the enzyme upward; consistent with this, serum ALP has been shown to predict survival specifically in patients with skeletal metastatic NPC

[25]. This is the clearest example of a liver enzyme that is, in practice, often reporting on bone. Recognising this, several groups have combined ALP with albumin: the albumin-to-alkaline-phosphatase ratio (AAPR) integrates hepatic and nutritional synthetic capacity in the numerator with tumour-and-bone burden in the denominator. In metastatic NPC treated with cisplatin-based chemotherapy, a low pretreatment AAPR (below approximately 0.447) was associated with significantly shorter overall and progression-free survival and correlated with higher LDH, behaving as an independent prognostic index [26].

5.5 Albumin and the synthetic axis

Albumin needs distinct attention as the marker most directly tied to hepatic synthetic function, although in cancer it is lowered as much by systemic inflammation and cachexia as by intrinsic liver disease. Low pretreatment albumin is associated with advanced disease and worse prognosis and has more discriminatory power when paired with other parameters than considered alone, as demonstrated by the AAPR work [26]. The greater lesson from these subsections is that no one enzyme is sufficient, but that a small panel of routinely measured indicators, interpreted with consideration of their tissue of origin, jointly refines the prognostic estimate achievable with staging.

Table 3. Summary of representative studies evaluating hepatic enzymes and liver-function indices as prognostic factors in nasopharyngeal carcinoma (first author, year, sample size, marker, reported cut-off, principal survival outcome).

Study (first author, year)	n	Marker	Reported cut-off	Principal survival outcome
Zhang M, 2016 [15]	Meta-analysis	Pretreatment LDH	Variable (≈ 200 – 250 IU/L)	High LDH associated with poorer OS, DMFS and DFS
Zhou GQ, 2016 [16]	NR	Pre- and post-treatment LDH (IMRT cohort)	NR	Elevated pre- and post-RT LDH predicted distant metastasis and shorter OS
Ali WAS, 2023 [17]	NR	Pretreatment LDH + number of metastatic sites	NR	Helped distinguish patients more or less likely to benefit from anti-PD-1 therapy
Wen YF, 2017 [18]	222	Pretreatment GGT	High vs low (NR)	High GGT associated with worse 3-yr OS, PFS, LRRFS and DMFS; independent of TNM stage
Luo M, 2017 [19]	374	Pretreatment GGT	≈ 23 U/L	High GGT was an independent predictor of shorter LRFS, PFS and OS
Wu J, 2019 [20]	NR	De Ritis (AST/ALT) ratio	NR	High ratio predicted poorer prognosis in nonmetastatic NPC
Xie Y, 2014 [23]	NR	Pretreatment ALP	NR	High ALP associated with advanced T classification/stage and poorer OS and tumour-free survival
Li G, 2012 [24]	NR	Pretreatment LDH + ALP	NR	Elevation of both behaved as poor prognostic factors
Jin Y, 2015 [25]	NR	ALP (skeletal-metastatic NPC)	NR	ALP predicted survival in patients with skeletal metastasis
Nie M, 2017 [26]	NR	AAPR (albumin / ALP)	≈ 0.447 (low)	Low AAPR associated with shorter OS and PFS; independent index; correlated with higher LDH
Liang L, 2023 [14]	NR	LFT nomogram (ALT, AST/ALT, LDH)	N/A (nomogram)	Predicted PFS under PD-1 therapy more accurately than TNM stage alone

OS, overall survival; PFS, progression-free survival; DFS, disease-free survival; DMFS, distant-metastasis-free survival; LRFS, local-recurrence-free survival; LRRFS, locoregional-relapse-free survival; RT, radiotherapy; IMRT, intensity-modulated radiotherapy; AAPR, albumin-to-alkaline-phosphatase ratio; LFT, liver function test; NR, not reported. Bracketed numbers correspond to the reference list.

PRINCIPAL SERUM BIOMARKERS IN NASOPHARYNGEAL CARCINOMA (NPC) PROGNOSIS

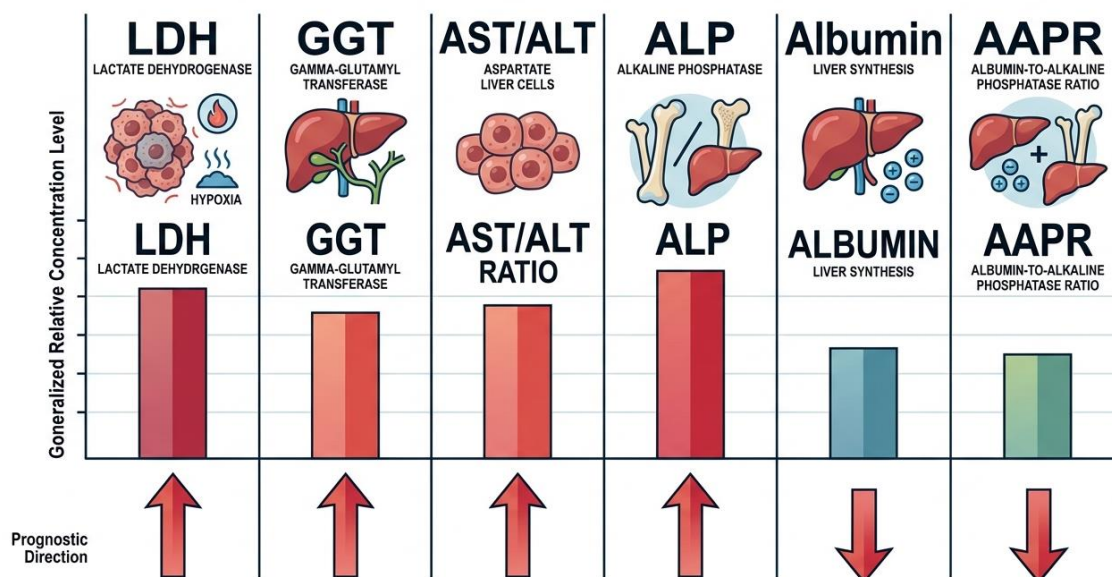


Figure 2. Illustrated comparison of the principal serum biomarkers (LDH, GGT, AST/ALT ratio, ALP, albumin/AAPR) showing their dominant biological source and the reported direction of their association with survival in NPC.

6. CLINICAL IMPLICATIONS AND MONITORING

Pulling the mechanistic and prognostic strands together yields a few reasonably concrete clinical messages. First, baseline liver chemistry and viral serology are not optional in NPC, particularly in endemic and Middle Eastern settings. Screening for hepatitis B surface antigen, and, where feasible, baseline HBV DNA, before starting chemotherapy identifies the patients who stand to benefit from antiviral prophylaxis, an intervention with demonstrated capacity to prevent reactivation and to keep treatment on schedule [11,12]. Second, a baseline panel that includes LDH, GGT, AST and ALT, ALP, albumin, and bilirubin provides both a prognostic snapshot and a reference against which on-treatment changes can be judged [15,18,20,23,26]. Because these markers are already part of routine pre-treatment work-up, capturing their prognostic value costs essentially nothing.

Third, interpretation of abnormal liver chemistry during treatment should be deliberately structured rather than reflexive. A rise in transaminases invites a short differential, namely drug toxicity, HBV reactivation, immune-related hepatitis under PD-1 therapy, or hepatic progression, and the appropriate response differs sharply among them: dose modification for cytotoxic toxicity, antiviral escalation for reactivation, corticosteroids for immune hepatitis, and a change of systemic strategy for progression [10,13,14]. Misclassifying progression as toxicity, or vice versa, can compromise either safety or tumour control. Fourth, dynamic monitoring adds value: serial LDH around radiotherapy, and longitudinal liver chemistry alongside plasma EBV DNA during follow-up, can flag distant relapse, frequently hepatic, earlier than symptoms would [3,16]. None of this replaces imaging, but it sharpens the clinician's index of suspicion and helps target it.

7. LIMITATIONS OF THE CURRENT EVIDENCE AND FUTURE DIRECTIONS

The enthusiasm for these markers should be tempered by an honest look at the evidence base. Almost all of the prognostic studies are retrospective and single-institution, which exposes them to selection bias and to the optimism that accompanies post-hoc cut-off selection. The cut-offs themselves are a real problem. Values for LDH, GGT, ALP and the De Ritis ratio vary from study to study, often derived by data-driven receiver-operating-characteristic optimisation in the same cohort in which they are tested. This inflates apparent performance and hinders external comparison. The literature is also geographically biased, with cohorts from Southern China dominating. Whether the same thresholds and hazard ratios apply in North African, Middle Eastern or Western populations where viral epidemiology, host genetics and histological mix differ has been little examined and should not be assumed. Moreover, there is surprisingly little research that separates the source of a specific anomaly so that bone-derived ALP and liver-derived ALP are often combined.

Several directions would strengthen the field. Prospective validation of pre-specified cut-offs in multicentre, ethnically diverse cohorts is the obvious priority. Composite models that combine biochemical markers with EBV DNA, imaging, and stage, of which the recent PD-1 nomogram is an early example [14], are likely to outperform any single analyte and deserve external testing. Standardised reporting of liver-event attribution during immunotherapy would clarify the still-thin NPC-specific picture of immune hepatitis. Finally, exploring the biology behind these associations, especially the metabolic basis of the LDH, GGT, and De Ritis signals, may convert prognostic correlation into actionable mechanism.

8. CONCLUSION

Liver function abnormalities in nasopharyngeal carcinoma are common, mechanistically heterogeneous, and clinically consequential, yet they are too often treated as incidental noise. This review has proposed that we should interpret them more discriminately. Abnormal liver tests in an NPC patient may indicate liver metastasis, reactivation of chronic hepatitis B during cytotoxic therapy, platinum-induced hepatocellular injury or immune-mediated hepatitis under checkpoint blockade and their management implications are totally different. In addition, a constellation of routinely measured, inexpensive markers led by LDH and including GGT, the De Ritis ratio, alkaline phosphatase, albumin and the albumin-to-alkaline-phosphatase ratio has prognostic information that is at least partly independent of TNM stage and that becomes more powerful when combined. The major limitation is methodological. Most data is retrospective, cut-offs are uneven and validation outside Southern China is sparse. The most important next steps are prospective, multicentre and ethnically diverse investigations that lock down thresholds and include these indicators in composite predictive models. Low-cost, high-yield practice supported by current data includes baseline hepatic chemistry and viral screening, systematic interpretation of on-treatment changes, and dynamic monitoring together with EBV DNA.

CONFLICTS OF INTEREST. The authors declare that they have no conflicts of interest.

ETHICAL APPROVAL. Not applicable.

FUNDING. Not applicable.

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