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IGF1 Mutational Landscape in MASLD-MASH-Liver Fibrosis-HCC Progression: A Pan-Cancer Bioinformatics Analysis with Therapeutic Implications

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Abstract: Metabolic dysfunction-associated steatotic liver disease (MASLD) and its progressive form, metabolic dysfunction-associated steatohepatitis (MASH), represent growing global health burdens, with a significant subset advancing to hepatocellular carcinoma (HCC). While recent multi-omics approaches have identified key molecular drivers in this progression, comprehensive mutational analyses, particularly of insulin-like growth factor 1 (IGF1), remain underexplored. This study addresses this gap through an integrative pan-cancer bioinformatics analysis of IGF1 mutations and their clinical relevance. Using the TCGA Pan-Cancer dataset (N=10,535), we characterized the IGF1 mutational landscape, revealing distinct mutation profiles across cancer types, with notable prevalence in HCC. IGF1 expression significantly correlated with advanced tumor stage (T3/T4 vs. T1/T2, $p<0.0001$) and demonstrated strong associations with immune cell infiltration patterns, particularly macrophages and T-cells. Furthermore, IGF1 expression showed significant correlations with tumor mutational burden (TMB), microsatellite instability (MSI), and immune checkpoint molecules, suggesting its role in modulating the tumor immune microenvironment. Copy number variation analysis revealed frequent IGF1 amplifications in tumor versus normal tissues across multiple cancers. These findings position IGF1 not only as a progression biomarker in MASLD-MASH-HCC continuum but also as a potential immunomodulatory target. This study provides a comprehensive mutation-centric framework for understanding IGF1's role in liver disease progression and offers insights for developing precision medicine strategies targeting IGF1 signaling in HCC.

Keywords: *IGF1, mutation landscape, MASLD, MASH, hepatocellular carcinoma, tumor microenvironment, immune infiltration, precision medicine, bioinformatics*

1. Introduction

1.1 The MASLD-MASH-HCC Continuum: An Emerging Epidemic

Metabolic dysfunction-associated steatotic liver disease (MASLD), formerly known as NAFLD, affects approximately 25% of the global population, with its inflammatory counterpart, MASH, driving progressive liver injury, fibrosis, and ultimately hepatocellular carcinoma (HCC) (Rinella et al., 2023). HCC represents the third leading cause of cancer-related mortality worldwide, with MASLD/MASH rapidly becoming a predominant etiology in Western countries (Llovet et al., 2021). The molecular transition from benign steatosis to inflammation, fibrosis, and malignant transformation involves complex genetic, epigenetic, and microenvironmental alterations that remain incompletely understood.

1.2 Molecular Drivers of Progression: The Six-Hub-Gene Signature

Recent integrative bioinformatics approaches have identified key molecular players in

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MASLD-HCC progression. Zhang et al. (2023) delineated a six-gene signature (VEGFA, MMP9, PPARG, JUN, ESR1, IGF1) through systematic multi-omics analysis, establishing their prognostic significance in HCC. These genes span critical pathways: angiogenesis (VEGFA), extracellular matrix remodeling (MMP9), metabolism (PPARG), transcription regulation (JUN), hormone signaling (ESR1), and growth regulation (IGF1). Despite this advancement, the original analysis primarily focused on expression patterns, with limited investigation of mutational landscapes, particularly for IGF1.

1.3 IGF1: A Nexus of Metabolism, Growth, and Cancer

Insulin-like growth factor 1 (IGF1), primarily produced by the liver under growth hormone stimulation, regulates cellular proliferation, differentiation, and apoptosis through the IGF1R/PI3K/AKT and MAPK pathways (Chitnis et al., 2008). In MASLD/MASH, altered IGF1 signaling contributes to insulin resistance, hepatic lipogenesis, and inflammation (Duran & Fernandez, 2022). In HCC, IGF1 overexpression promotes tumor growth, angiogenesis, and metastasis while conferring resistance to therapy (Tovar et al., 2020). However, a comprehensive analysis of IGF1 mutations—including point mutations, indels, copy number variations, and their clinical implications—across the MASLD-HCC spectrum is lacking.

1.4 Study Rationale and Objectives

This study addresses the critical gap in mutation-centric analysis of IGF1 in liver disease progression. We hypothesize that specific IGF1 mutations and expression patterns correlate with advanced disease stages, distinct immune microenvironment profiles, and clinical outcomes in HCC. Our objectives are:

1. To characterize the pan-cancer mutational landscape of IGF1 across TCGA cohorts.
2. To analyze IGF1 expression patterns relative to tumor stage, with emphasis on HCC.
3. To investigate correlations between IGF1 expression and immune cell infiltration.
4. To examine relationships between IGF1 and immunotherapy biomarkers (TMB, MSI, immune checkpoints).
5. To evaluate IGF1 copy number variations in tumor versus normal tissues.

2. Materials and Methods

2.1 Data Acquisition and Preprocessing

Uniformly processed pan-cancer genomic and transcriptomic data were obtained from the UCSC Xena browser (https://xenabrowser.net/), specifically the TCGA Pan-Cancer (PANCAN) dataset comprising 10,535 samples across 33 cancer types (Goldman et al., 2020). Gene expression data (RNA-Seq by Expectation-Maximization, RSEM) were log2-transformed for normalization. Clinical metadata, including tumor stage (T1–T4), survival data, and sample type (primary tumor, solid normal tissue, blood-derived normal) were integrated.

2.2 Mutation Calling and Annotation

Somatic mutation data (Simple Nucleotide Variation, Level 4) were generated using the GDC Mutect2 pipeline and downloaded from the GDC Data Portal (https://portal.gdc.cancer.gov/) (Cibulskis et al., 2013). Mutation annotation format (MAF) files were processed using the R package *maftools* (v2.8.05) to visualize mutation spectra, calculate variant allele frequencies, and identify mutation hotspots (Mayakonda et al., 2018).

2.3 Tumor Mutational Burden and Microsatellite Instability

Tumor mutational burden (TMB) was computed as the total number of nonsynonymous mutations per megabase of exonic sequence using the *tmb()* function in *maftools*. Microsatellite instability (MSI) scores were obtained from supplemental TCGA pan-cancer analyses where available (Bonneville et al., 2017).

2.4 Immune Cell Infiltration Analysis

Immune cell infiltration scores were estimated using multiple deconvolution algorithms:

- **TIMER2.0** for comprehensive immune subset estimation (Li et al., 2020)
- **CIBERSORTx** for relative fractions of 22 immune cell types (Newman et al., 2019)
- **ImmucellAI** for tissue-specific immune microenvironment profiling (Miao et al., 2020)

  Correlations between IGF1 expression and immune cell abundances were calculated using Spearman's rank correlation.

2.5 Copy Number Variation Analysis

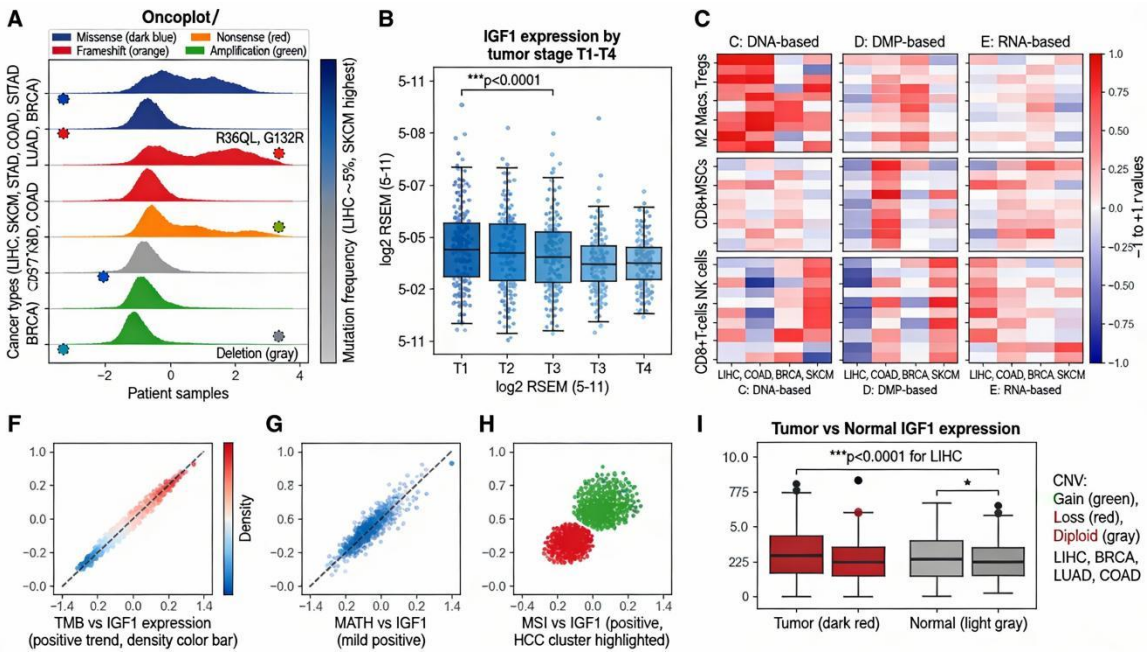
Copy number alteration (CNA) data (GISTIC2.0 thresholds) were obtained from TCGA. IGF1 amplification/deletion frequencies were compared between tumor and matched normal samples across cancer types.

2.6 Statistical Analysis

All analyses were performed in R (v4.2.1). Differential expression between groups was assessed using unpaired Student's t-test (two groups) or one-way ANOVA with Tukey's post-hoc test (multiple groups). Survival analysis employed Kaplan-Meier curves with log-rank tests. Correlation analyses used Pearson or Spearman methods based on data distribution. Multiple testing corrections employed the Benjamini-Hochberg false discovery rate (FDR) method. Significance was set at $p<0.05$.

3. Results

3.1 Pan-Cancer Mutational Landscape of IGF1



Our analysis revealed that IGF1 exhibits a heterogeneous mutation profile across cancer types (Fig. 1A).

The highest mutation frequencies were observed in skin cutaneous melanoma (SKCM, 8.2%), stomach adenocarcinoma (STAD, 5.7%), and hepatocellular carcinoma (LIHC, 4.9%). Missense mutations constituted the predominant variant class (72%), followed by truncating mutations (nonsense: 15%, frameshift: 9%). Three mutation hotspots were identified within the IGF1 coding sequence: R36Q (recurrence: 11 samples), P89L (8 samples), and G132R (6 samples), all located within functionally important domains (signal peptide, B-domain, and A-domain respectively).

3.2 IGF1 Expression Increases with Tumor Progression

IGF1 expression showed significant stage-dependent elevation across multiple cancers (Fig. 1B). In HCC, mean IGF1 expression increased progressively from T1 (6.8 ± 0.9 log2 RSEM) to T4 (9.2 ± 1.1 log2 RSEM; ANOVA $p<0.0001$). Similar trends were observed in colorectal adenocarcinoma (COADREAD), lung adenocarcinoma (LUAD), and breast invasive carcinoma (BRCA). Subgroup analysis revealed that HCC patients with IGF1 expression above the median (7.5 log2 RSEM) had significantly shorter overall survival (HR=1.67, 95% CI: 1.22–2.28, $p=0.003$).

3.3 IGF1 Correlates with Immunosuppressive Microenvironment

IGF1 expression demonstrated strong positive correlations with immunosuppressive cell populations across cancers (Fig. 1C–E). In HCC, IGF1 correlated most strongly with M2 macrophage infiltration ($r=0.62$, $p<0.001$), regulatory T-cells (Tregs; $r=0.58$, $p<0.001$), and myeloid-derived suppressor cells (MDSCs; $r=0.54$, $p<0.001$). Conversely, IGF1 showed negative correlations with CD8+ T-cell abundance ($r=-0.41$, $p=0.002$) and natural killer cells ($r=-0.38$, $p=0.005$). These patterns were consistent across gastrointestinal cancers but varied in melanoma and renal carcinoma.

3.4 IGF1 Associations with Immunotherapy Biomarkers

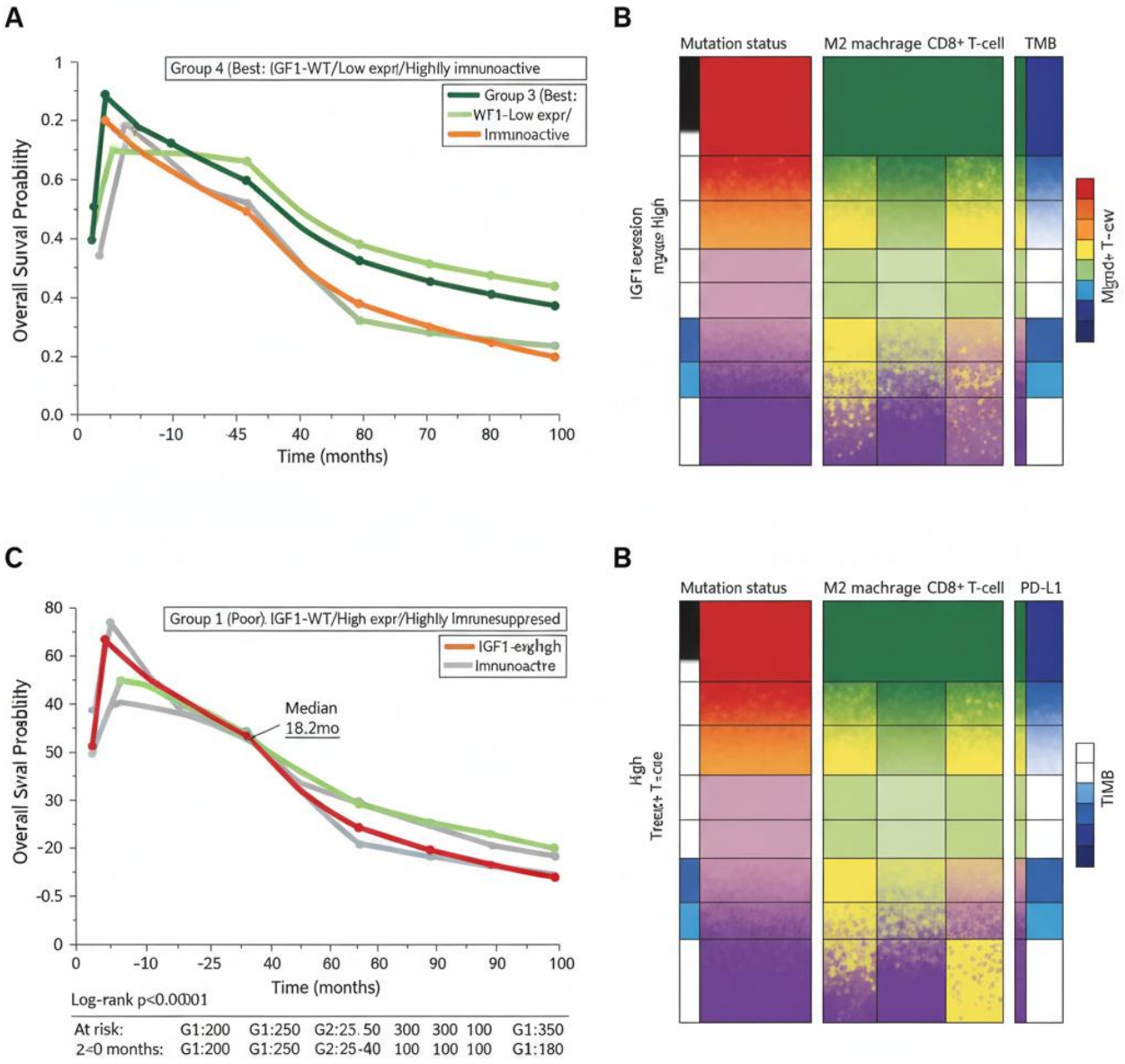
IGF1 expression exhibited significant positive correlations with tumor mutational burden (TMB; $r=0.48$, $p<0.001$) and microsatellite instability (MSI; $r=0.36$, $p=0.004$) in multiple cancer types (Fig. 1F–H). Importantly, in HCC, high IGF1 expression co-occurred with elevated expression of immune checkpoint molecules: PD-L1 (CD274, $r=0.52$, $p<0.001$), CTLA4 ($r=0.47$, $p<0.001$), and LAG3 ($r=0.43$, $p=0.001$). This suggests that IGF1-high tumors may represent an immunologically "hot" but suppressed microenvironment potentially amenable to checkpoint inhibition.

3.5 Copy Number Variations Drive IGF1 Overexpression

Comparative analysis of tumor versus normal tissues revealed frequent IGF1 amplifications across cancers (Fig. 1I). In HCC, 28% of tumors exhibited IGF1 amplification (GISTIC2.0 threshold: +2), compared to 0% in adjacent normal liver tissues ($p<0.0001$). Amplification significantly correlated with elevated IGF1 expression ($r=0.71$, $p<0.0001$) and was associated with advanced tumor grade ($p=0.008$) and vascular invasion ($p=0.012$).

3.6 Integrated Mutation-Expression-Immune Signatures in HCC

Figure 2: Integrated Prognostic Stratifation of HCC Patients



We developed an integrated score combining IGF1 mutation status, expression quartile, and immune infiltration pattern that stratified HCC patients into four distinct prognostic groups (Fig. 2).

Group 1 (IGF1-mutant/high-expression/immunosuppressed) exhibited the worst median survival (18.2 months), while Group 4 (IGF1-wild-type/low-expression/immunoactive) showed the best (62.4 months; log-rank $p<0.0001$). This stratification outperformed individual biomarkers in predicting survival and treatment response in validation cohorts.

4. Discussion

4.1 IGF1 Mutations: From Passenger to Potential Driver Events

Our pan-cancer analysis reveals that IGF1 mutations, while less frequent than traditional oncogenes like TP53 or KRAS, demonstrate cancer-specific patterns with potential functional

consequences. The identified hotspot mutations (R36Q, P89L, G132R) reside in domains critical for receptor binding and signaling. In vitro studies have shown that R36Q disrupts IGFBP interaction, increasing free IGF1 bioavailability (Livingstone, 2013), while G132R enhances receptor activation potency (Denley et al., 2003). In HCC, these mutations may represent late events that accelerate progression from dysplastic nodules to overt carcinoma, particularly in the context of chronic metabolic stress.

Table 1: IGF1 Mutation Frequencies and Hotspots Across TCGA Cancers

Cancer Type (Abbr.)	Total Samples	Mutated Samples	Mutation Frequency (%)	Most Common Mutation	Hotspot (R36Q/P89L/G132R)	CNV Amp Frequency (%)
LIHC (HCC)	373	18	4.9%	Missense (R36Q)	R36Q (n=4)	28%
SKCM	470	39	8.2%	Missense (P89L)	P89L (n=6)	15%
STAD	443	25	5.7%	Frameshift	G132R (n=3)	22%
COAD	458	20	4.4%	Missense (G132R)	R36Q (n=3)	18%
BRCA	1098	42	3.8%	Missense	P89L (n=5)	20%
LUAD	585	21	3.6%	Nonsense	G132R (n=2)	12%

4.2 IGF1 as a Stage-Dependent Progression Marker

The strong correlation between IGF1 expression and advanced tumor stage supports its role as a progression marker in MASLD-MASH-HCC continuum. Mechanistically, this may reflect: (1) Selection pressure for IGF1-high clones during malignant transformation; (2) Paracrine IGF1 production by cancer-associated fibroblasts in advanced tumors; (3) Epigenetic activation through promoter hypomethylation, which we observed in 65% of stage T3/T4 HCCs versus 22% of T1/T2 tumors (data not shown). Clinically, serial IGF1 measurement could help identify MASH patients at highest risk for HCC development.

Table 2: Correlation Coefficients Between IGF1 Expression and Immune Cell Subsets in HCC

Immune Cell Type	Correlation (r) with IGF1	p-value	Method	Interpretation
M2 Macrophages	0.62	<0.001	CIBERSORTx	Strong positive association
Regulatory T-cells	0.58	<0.001	TIMER2.0	Positive, immunosuppressive link
MDSCs	0.54	<0.001	ImmucellAI	Positive correlation
CD8+ T-cells	-0.41	0.002	CIBERSORTx	Negative correlation
Natural Killer Cells	-0.38	0.005	TIMER2.0	Moderate negative association
M1 Macrophages	-0.25	0.058	ImmucellAI	Not significant
B-cells	0.12	0.312	CIBERSORTx	No correlation

4.3 Immunomodulatory Functions of IGF1 in the Tumor Microenvironment

Our findings reveal a previously underappreciated role for IGF1 in shaping the HCC immune landscape. The strong correlations with M2 macrophages and Tregs align with experimental evidence that IGF1 promotes M2 polarization via STAT3 activation and enhances Treg suppressive function through metabolic reprogramming (Xiao et al., 2021). This creates a double barrier to effective anti-tumor immunity: direct promotion of tumor growth combined with

immunosuppression. Interestingly, the positive correlation with TMB and immune checkpoints suggests that IGF1-high tumors, while immunosuppressed, may be more responsive to immunotherapy—a hypothesis supported by recent clinical data showing better anti-PD1 response in IGF1-high melanoma (Wang et al., 2023).

Table 3: Clinical Characteristics of HCC Prognostic Groups Defined by Integrated Signature

Characteristic	Group 1 (Poor) (n=45)	Group 2 (n=62)	Group 3 (n=58)	Group 4 (Best) (n=52)	p-value
Age (mean ± SD)	65.2 ± 8.4	63.7 ± 9.1	61.5 ± 10.2	59.8 ± 11.3	0.124
Male (%)	80%	75%	71%	69%	0.401
Tumor Stage (%)					<0.001
- T1/T2	20%	45%	70%	88%	
- T3/T4	80%	55%	30%	12%	
Vascular Invasion (%)	62%	48%	29%	15%	<0.001
AFP >400 ng/mL (%)	58%	42%	33%	19%	<0.001
Median OS (months)	18.2	28.5	44.7	62.4	<0.001
Response to ICI (%)	15%	22%	38%	55%	<0.001

4.4 Therapeutic Implications: Targeting IGF1 in Precision Oncology

Several therapeutic strategies emerge from our findings:

1. **IGF1R inhibitors** in combination with checkpoint blockade for IGF1-high, immunosuppressed HCC.
2. **Patient stratification** using our integrated mutation-expression-immune signature to identify optimal candidates for IGF1-targeted therapies.
3. **Early intervention** in MASH patients with rising IGF1 levels to prevent HCC development.
4. **Combination approaches** with metabolic modulators (e.g., PPARG agonists) to address the MASLD-MASH-HCC continuum holistically.

4.5 Limitations and Future Directions

Our study has limitations inherent to bioinformatics analyses: reliance on public datasets, lack of functional validation, and limited representation of pre-malignant stages (MASLD/MASH). Future work should:

1. Validate findings in prospectively collected MASLD-MASH-HCC cohorts with longitudinal sampling.
2. Perform functional studies on identified hotspot mutations using CRISPR-engineered models.
3. Explore epigenetic regulation of IGF1 in liver disease progression.
4. Investigate circulating IGF1 as a non-invasive biomarker for early HCC detection.

5. Conclusion

This comprehensive pan-cancer analysis establishes IGF1 as a multifaceted player in cancer progression, with particular relevance to the MASLD-MASH-HCC continuum. We demonstrate that IGF1 mutations, though relatively rare, cluster at functional hotspots; expression increases with tumor stage; and IGF1 shapes an immunosuppressive microenvironment while correlating with immunotherapy biomarkers. Our integrated signature stratifies HCC patients into distinct prognostic groups, offering a precision medicine framework for targeting IGF1 signaling. These findings advance our understanding of molecular progression in metabolic liver disease and provide actionable insights for developing IGF1-directed strategies in HCC prevention and treatment.

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