Table 2: Various HCC biomarkers and their clinical use.

HCC marker	Clinical use
Alpha-fetoprotein	Early diagnosis, monitoring, and recurrence
Lens culinaris agglutinin reactive AFP (AFP-L3%)	Early diagnosis and prognosis, vascular invasion
Des-gamma-carboxy prothrombin (DCP)	Early diagnosis and prognosis, portal vein invasion and metastasis
Gamma-glutamyl transferase	Early diagnosis complementary to other markers
Alpha-l-fucosidase	Early diagnosis
Glypican-3	Early diagnosis
Human carbonyl reductase 2	Prognosis
Golgi phosphoprotein 2	Tumor aggressiveness
Transforming growth factor beta	Tumor invasiveness
Hepatocyte growth factor (HGF)	Prognosis and disease recurrence
Transforming growth factor-b (TGF-b)	Prognosis invasiveness
Tumor specific growth factor	Diagnosis complementary to other markers
Epidermal growth factor receptor family	Early recurrence
Hepatocyte growth factor	Metastasis reduced survival
Micro RNAs	Tumor spread and survival

2.5. Pathological Biomarkers. Finally there have been reports of pathological biomarkers of HCC for diagnosis and prognosis. Some of these diagnostic biomarkers focus on immunochemical staining patterns to distinguish high-grade dysplastic nodules and well-differentiated HCC. The best type of immunostaining for this difficult condition has been reported to be the combination of heat-shock protein 70 (HSP70), glypican-3 (GPC3), and glutamine synthetase (GS). For prognostic use a number of histological and immuno-histochemical markers such as markers of cell proliferation (Ki67), apoptosis or cell survival (survivin), cell adhesion molecules (E-cadherin), neoangiogeneis (VEGF), and more have been looked in small studies showing promise; however, most of these markers have not been validated in large studies [57]. Various HCC biomarkers and their clinical use have been summarized in Table 2.

3. Discussion

Hepatocarcinogenesis is a complex multistate process usually occurring after many years of chronic exposure to several mitogenic and mutagenic environments precipitating random genetic alterations. Recent evidence suggest that intrinsic biologic characteristics of the tumor in terms of proliferation and invasiveness are probably related to different composition and activity of the microenvironment, leading to very different clinical outcomes. HCC is rather unique with its ability to synthesize various tumor-related proteins rendering itself more suitable to biomarker-related research than other tumors. Because of the large multitude of biomarkers reported in this disease, selecting the biomarkers which would be most useful in clinical practice has been more than challenging. In this rather brief overview, we tried to focus on most widely used and accepted biomarkers.

Despite its limitations, serum AFP still remains the most widely used tumor marker in clinical practice. Recent research favors the circulating hepatoma-specific AFP subfraction AFP-L3 and DCP over AFP alone in differentiating HCC from nonmalignant hepatopathy and detecting small HCC. Furthermore, some other tumor markers, such as GPC3, GGT II, AFU, have been shown to be supplementary to AFP and DCP in the detection of HCC. Some of them even can be detected in HCC patients seronegative for both AFP and DCP, thus indicating that the simultaneous determination of these markers may improve the accuracy.

However, most exciting and promising area of research in this disease has been the identification of a new group of molecules called miRNAs. MiRNAs have been discovered to be aberrantly expressed in HCC, and some of them are functionally involved in HCC carcinogenesis and progression. Furthermore, certain microRNAs are associated with HCC or related to HCC subtypes, implicating the potential use of microRNAs in HCC patient stratification of diagnosis and prognosis. Some of these HCC-associated miRNAs have been validated in independent cohorts. This brings the possibility of developing clinically useful platforms to develop HCC diagnosis, risk assessment, and patient risk stratification with the ultimate goal of personalized therapy.

4. Conclusion

Research into the molecular biology of hepatocarcinogenesis has identified numerous biomarkers which could provide additional information for HCC biologic behavior metastasis and recurrence to that gained from traditional histopathological features. A large number of biomarkers have been shown to have potential predictive significance. However, most of them have been studied retrospectively. Efforts should be directed towards prospective clinical trials in evaluating the prognostic significance of these markers. These molecules not only help in prediction of prognosis for patients with HCC but may also assist in deciding appropriate