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REVIEW

Understanding and targeting resistance mechanisms in cancer

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Abstract

Resistance to cancer therapies has been a commonly observed phenomenon in clinical practice, which is one of the major causes of treatment failure and poor patient survival. The reduced responsiveness of cancer cells is a multifaceted phenomenon that can arise from genetic, epigenetic, and microenvironmental factors. Various mechanisms have been discovered and extensively studied, including drug inactivation, reduced intracellular drug accumulation by reduced uptake or increased efflux, drug target alteration, activation of compensatory pathways for cell survival, regulation of DNA repair and cell death, tumor plasticity, and the regulation from tumor microenvironments (TMEs). To overcome cancer resistance, a variety of strategies have been proposed, which are designed to enhance the effectiveness of cancer treatment or reduce drug resistance. These include identifying biomarkers that can predict drug response and resistance, identifying new targets, developing new targeted drugs, combination therapies targeting multiple signaling pathways, and modulating the TME. The present article focuses on the different mechanisms of drug resistance in cancer and the corresponding tackling approaches with recent updates. Perspectives on polytherapy targeting multiple resistance mechanisms, novel nanoparticle delivery systems, and advanced drug design tools for overcoming resistance are also reviewed.

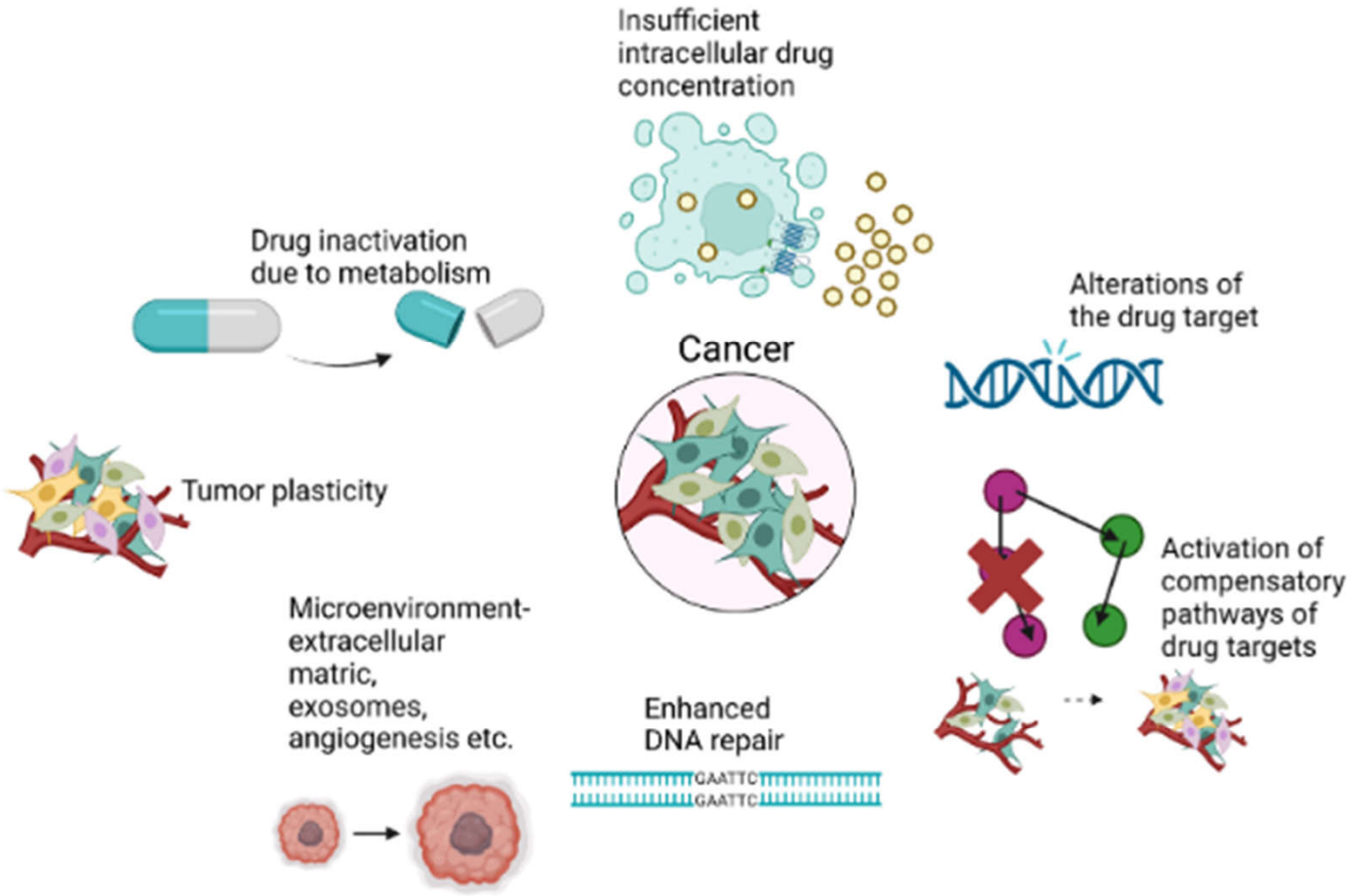

FIGURE 1 Cancer resistance mechanisms, including drug inactivation, insufficient intracellular drug concentration, drug target alterations, compensatory pathways activation, DNA repair enhancement, and tumor plasticity. *Source*: This figure was created with Biorender.com.

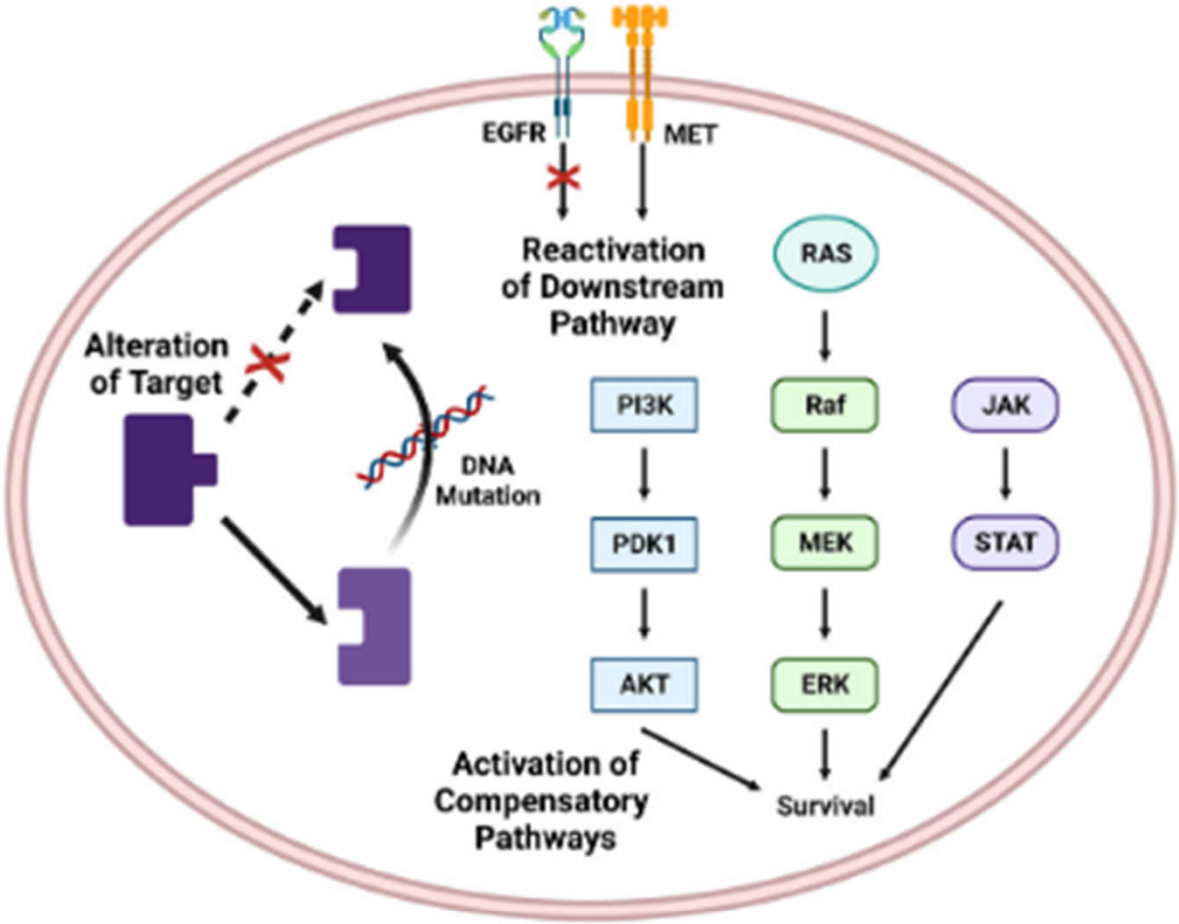

FIGURE 2 Alteration of drug target and activation of compensating pathways. Cancer resistance associated with alterations in the drug target site or modifications in the structure of the target. The reactivation of the downstream pathway bypasses the other unblocked pathway enabling drug resistance. Activation of compensatory signaling pathways to resist cell death leading to drug resistance. *Source*: This figure was created with Biorender.com.

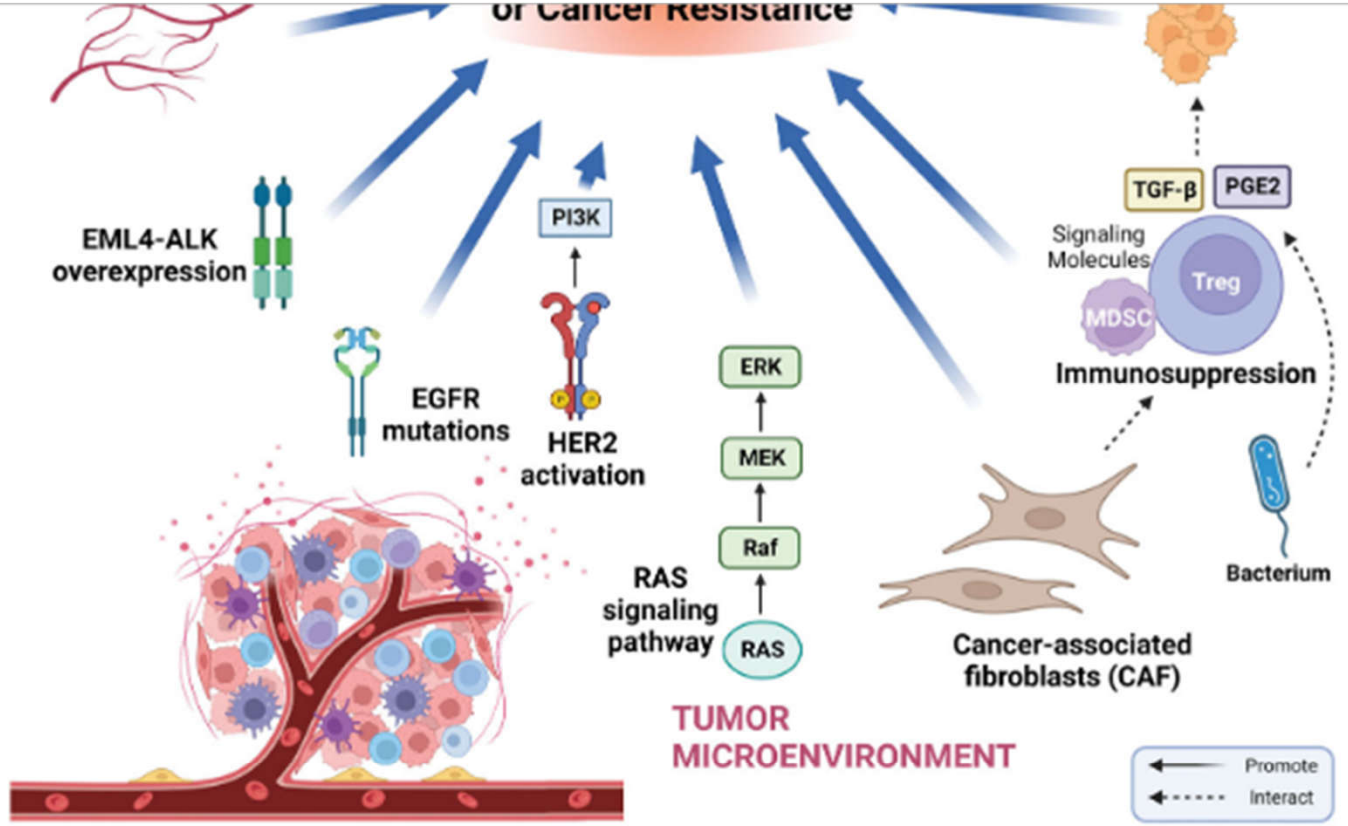

FIGURE 3 Adaptive mechanisms of cancer cell survival and cancer resistance driven by tumor microenvironment (TME). The TME is important for cancer resistance; the cancer cells within the TME can undergo a series of adaptive changes, such as various cellular components can complement the growth signal of cancer cells, combining with angiogenesis to promote cell survival and resistance. The immunosuppression caused by the TME prevents immune cells from killing cancer cells. The induction of the TGF-β signaling and the release of prostaglandin E2 (PGE2) resulting in further augmentation of self-renewal and plasticity of cancer stem cells (CSCs). *Source*: This figure was created with Biorender.com.

TABLE 1 Cancer combination therapies approved or in clinical trials in the recent 5 years.

Combination therapy	Target cancer type	Approval date/Clinical trials process
Tremelimumab + durvalumab + platinum-based chemotherapy	Adult patients with metastatic NSCLC with no sensitizing EGFR mutation or ALK genomic cancer aberrations	November 10, 2022 (NCT03164616)
Brentuximab vedotin + doxorubicin + vincristine + etoposide + prednisone + cyclophosphamide	Pediatric patients 2 years of age and older with previously untreated high risk cHL	November 10, 2022 (NCT03755804)
Cemiplimab-rwlc + platinum-based chemotherapy	Adult patients with advanced NSCLC with no EGFR, ALK, or ROS1 aberrations	November 8, 2022 (NCT03409614)
Tremelimumab + durvalumab	Adult patients with uHCC	October 21, 2022 (NCT03298451)
Durvalumab + gemcitabine + cisplatin	Adult patients with locally advanced or metastatic BTC	September 2, 2022 (NCT03875235)
Darolutamide + docetaxel	Adult patients with mHSPC	August 5, 2022 (NCT02799602)
Dabrafenib + trametinib	Adult and pediatric patients ≥6 years of age with unresectable or metastatic solid cancers with BRAF V600E mutation	Accelerated Approval June 22, 2022 (NCT02034110, NCT02465060, NCT02124772, original projected completion: October 21, 2028)
Nivolumab + fluoropyrimidine- and platinum-based chemotherapy	Patients with advanced or metastatic ESCC	May 27, 2022 (NCT03143153)
Nivolumab + ipilimumab	Patients with advanced or metastatic ESCC	May 27, 2022 (NCT03143153)
Ivosidenib + azacitidine (azacitidine for	Newly diagnosed AML with a susceptible	May 25, 2022 (NCT03173248)

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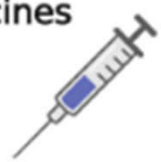
Combating drug resistance in cancer

Combination therapy with nonoverlapping mechanism of action

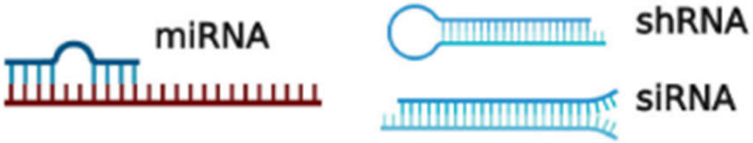
Checkpoint blockade immunotherapy

Anti-CTLA-4
Anti-PD-(L)1

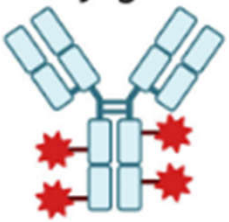
Tumor Vaccines



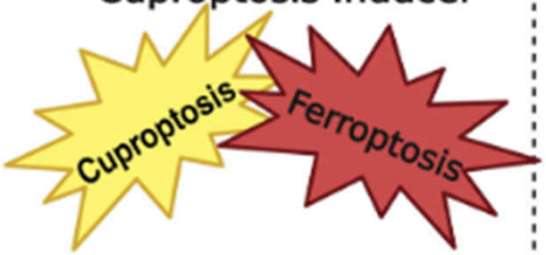
Gene therapy



Antibody-Drug-Conjugates



Ferroptosis and Cuproptosis Inducer



Development of Novel Drugs Targeting CSC and EMT

Epithelial Mesenchymal Transition

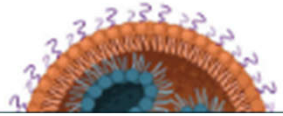
Cancer Stem Cell

Targeted therapy

ABC transporters inhibitors

Modulators of cancer cell proliferation and apoptosis

Lipid Nanoparticle



combinations after the emergence of resistance will significantly accelerate the development of more effective therapeutic combinations to reverse the MDR in cancer cells (Figure 4).

4 | CONCLUSION

As summarized in Table 2, MDR in cancer is a multifactorial phenomenon that results in drug inactivation, efflux, target alteration, cancer cell death inhibition, DNA damage repair, cellular heterogeneity, and more. Tumor drug resistance has become a significant problem in oncology, affecting the treatment effect and prognosis of cancer patients, and may lead to tumor progression or even recurrence. Therefore, it becomes crucial to understand the causes and underlying mechanisms of cancer drug resistance, which will facilitate the development of various therapies or combinations for treating different cancers. Combination therapy is considered the most important

treatment option for personalized medicine and overcoming MDR. Simultaneous use of two or more treatment methods can effectively overcome MDR, avoid clinical toxicity, and improve patients' survival rate and quality of life. The specificity of cancer cells is a promising research and therapeutic area, which will help to develop tumor-targeted therapies with low toxicity to normal cells and

2. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71(3):209-249.
3. Awan A, Esfahani K. Endocrine therapy for breast cancer in the primary care setting. *Curr Oncol*. 2018;25(4):285-291.
4. Kruger S, Ilmer M, Kobold S, et al. Advances in cancer immunotherapy 2019 – latest trends. *J Exp Clin Cancer Res*

NEWS RELEASE 23-MAY-2023

Fever found to be most common non-respiratory feature of SARS-CoV-2 infection

Meeting Announcement

AMERICAN THORACIC SOCIETY

Session: C58, Health Services Research in Diverse Settings

Date and Time: 11:30 a.m. ET, Tuesday, May 23, 2023

Location: WEWCC, Area 1, Hall C (Lower Level)

IMAGE: FEVER FOUND TO BE THE MOST COMMO NON-RESPIRATORY FEATURE OF COVID-19 INFECTION. view more >

CREDIT: ATS

ATS 2023, Washington, DC – Fever was found to be the most common non-respiratory feature of infection with SARS-CoV-2, the virus that causes COVID-19, according to research published at the ATS 2023 International Conference. The finding held true regardless of which COVID variant patients had, and whether or not they were

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REVIEW

NAFLD-related hepatocellular carcinoma: The growing challenge

Pir Ahmad Shah[1] | Rashmee Patil[2] | Stephen A. Harrison[3]

Abstract

Hepatocellular carcinoma (HCC) is a common cause of cancer-related mortality and morbidity worldwide. With the obesity pandemic, NAFLD-related HCC is contributing to the burden of disease exponentially. Genetic predisposition and clinical risk factors for NAFLD-related HCC have been identified. Cirrhosis is a well-known and major risk factor for NAFLD-related HCC. However, the occurrence of NAFLD-related HCC in patients without cirrhosis is increasingly recognized and poses a significant challenge regarding cancer surveillance. It is of paramount importance to develop optimal risk stratification scores and models to identify subsets of the population at high risk so they can be enrolled in surveillance programs. In this review, we will discuss the risks and prediction models for NAFLD-related HCC.

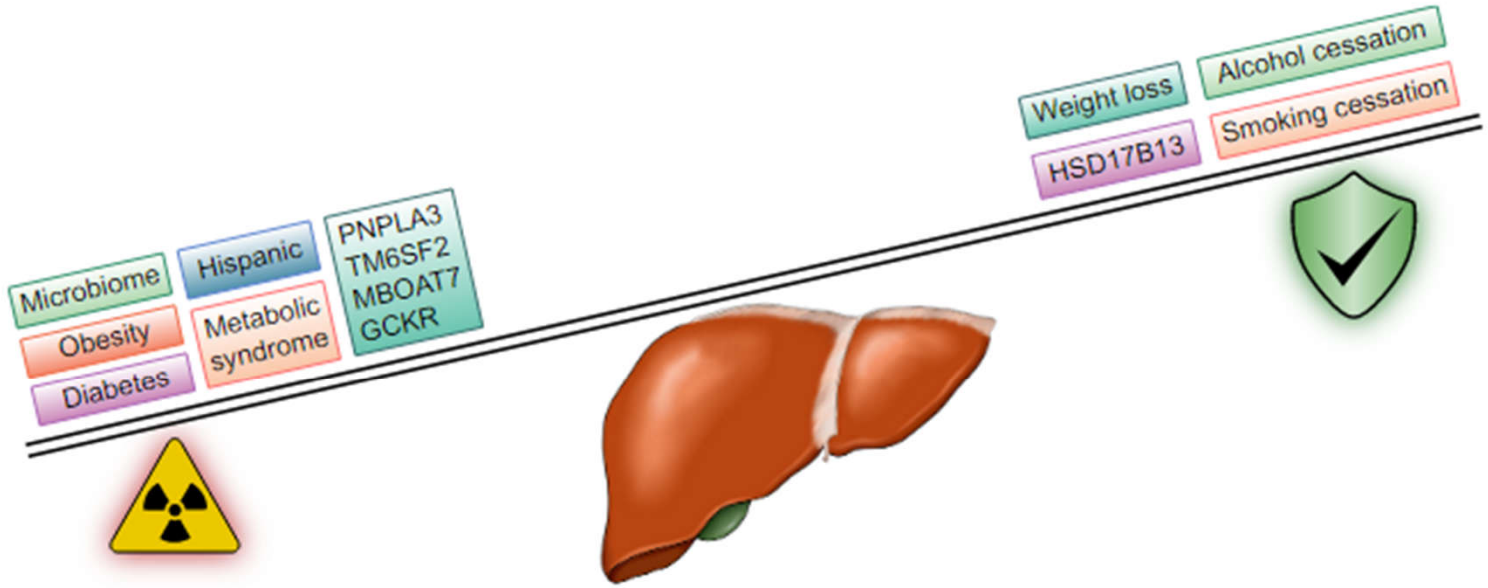
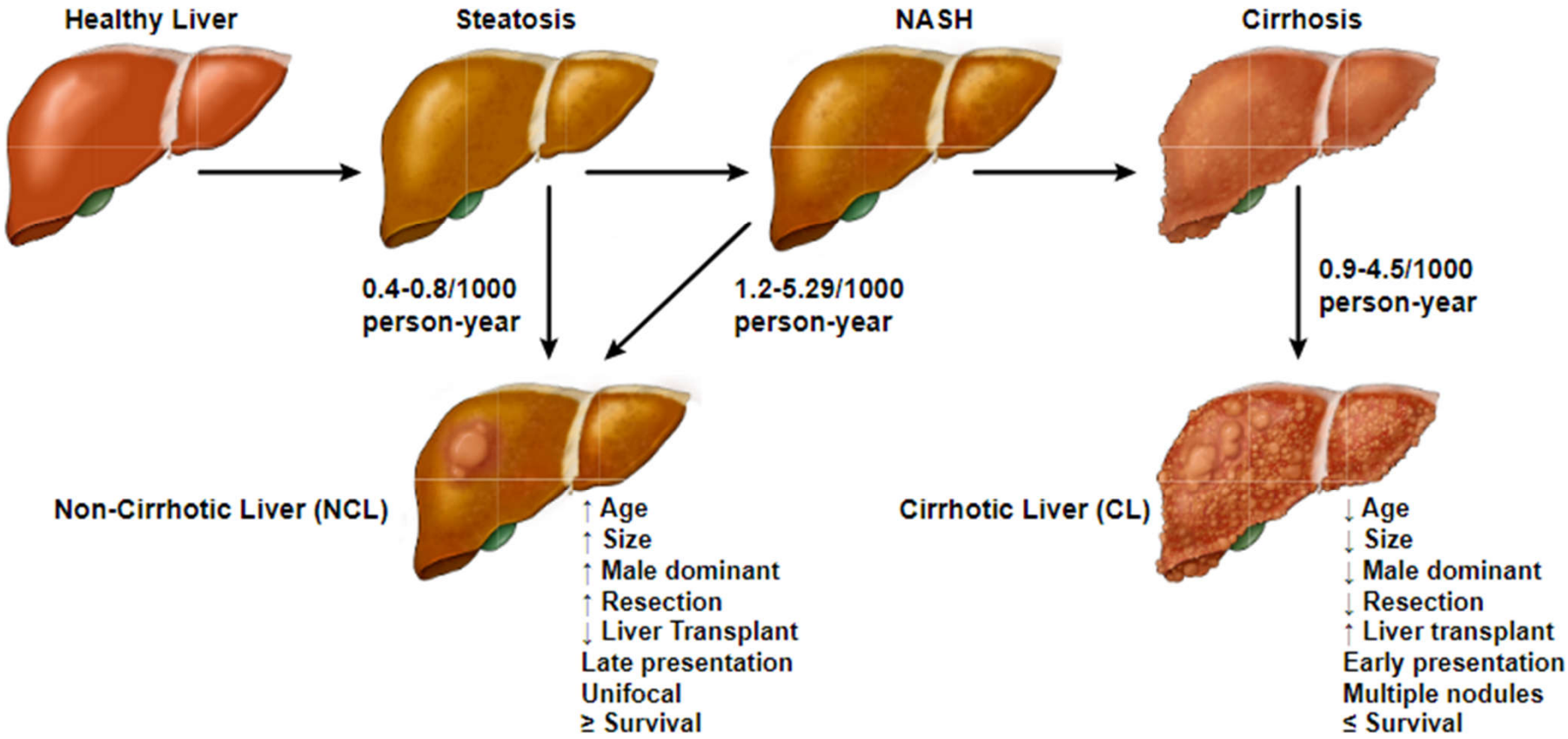


FIGURE 2 Risk and protective factors for NAFLD-related hepatocellular carcinoma (HCC). GCKR, glucokinase regulator; HSD17B13, 17-β hydroxysteroid dehydrogenase 13; MBOAT7, membrane bound O-acyltransferase domain-containing 7; PNPLA3; patatin-like phospholipase domain-containing 3; TM6SF2, transmembrane 6 superfamily member 2.


Healthy Liver
Steatosis
NASH
Cirrhosis
0.4-0.8/1000
person-year
1.2-5.29/1000
person-year
0.9-4.5/1000
person-year
Non-Cirrhotic Liver (NCL)
↑ Age
↑ Size
↑ Male dominant
↑ Resection
↓ Liver Transplant
Late presentation
Unifocal
≥ Survival
Cirrhotic Liver (CL)
↓ Age
↓ Size
↓ Male dominant
↓ Resection
↑ Liver transplant
Early presentation
Multiple nodules
≤ Survival

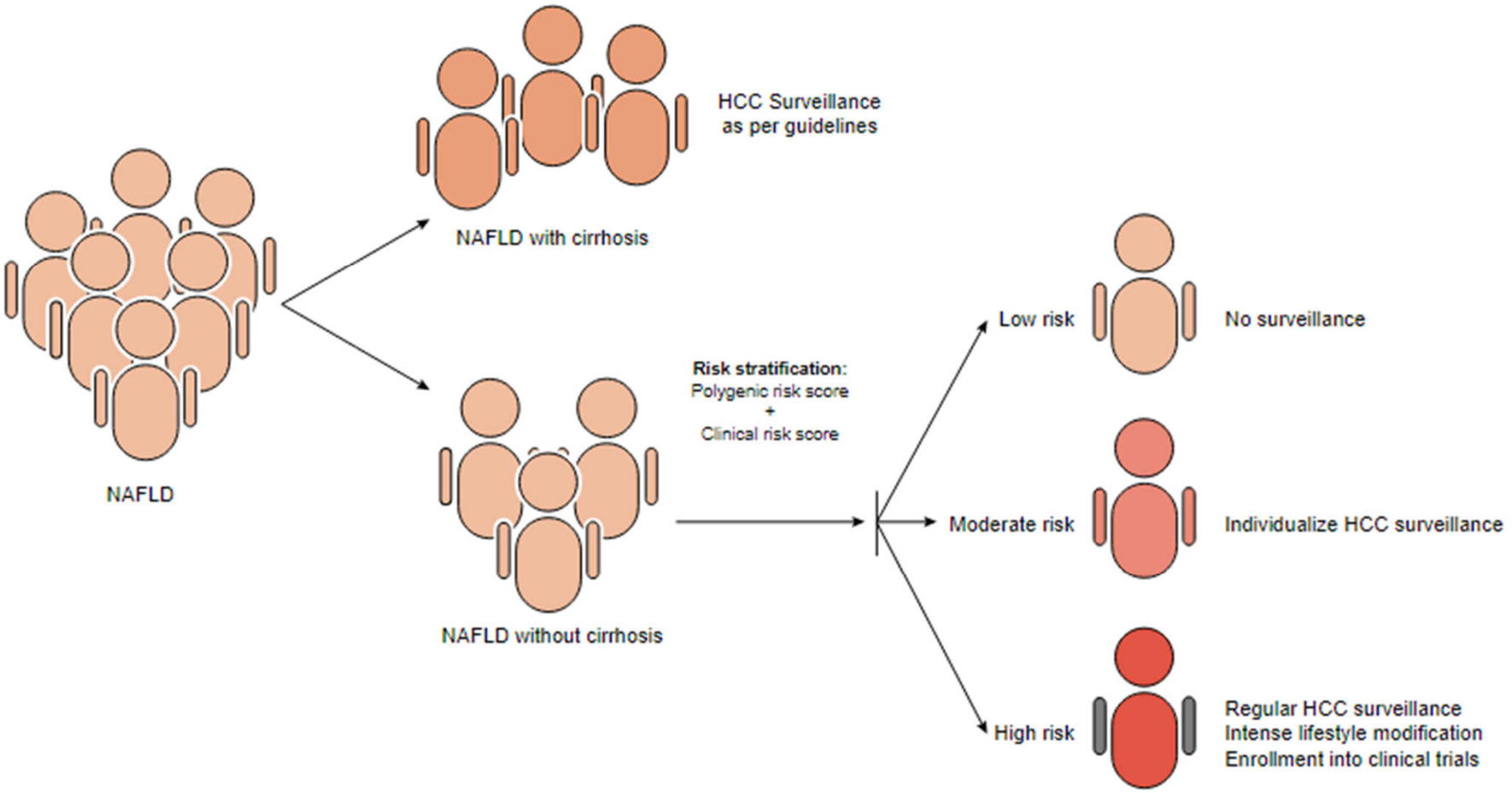


FIGURE 5 Model for risk stratification in NAFLD-related hepatocellular carcinoma (HCC).

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Acute and postacute sequelae associated with SARS-CoV-2 reinfection

Received: 12 June 2022

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Benjamin Bowe[1,2], Yan Xie[1,2] & Ziyad Al-Aly[1,2,3,4,5]

First infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is associated with increased risk of acute and postacute death and sequelae in various organ systems. Whether reinfection adds to risks incurred after first infection is unclear. Here we used the US Department of Veterans Affairs' national healthcare database to build a cohort of individuals with one SARS-CoV-2 infection (n = 443,588), reinfection (two or more infections, n = 40,947) and a noninfected control (n = 5,334,729). We used inverse probability-weighted survival models to estimate risks and 6-month burdens of death, hospitalization and incident sequelae. Compared to no reinfection, reinfection contributed additional risks of death (hazard ratio (HR) = 2.17, 95% confidence intervals (CI) 1.93–2.45), hospitalization (HR = 3.32, 95% CI 3.13–3.51) and sequelae including pulmonary, cardiovascular, hematological, diabetes, gastrointestinal, kidney, mental health, musculoskeletal and neurological disorders. The risks were evident regardless of vaccination status. The risks were most pronounced in the acute phase but persisted in the postacute phase at 6 months. Compared to noninfected controls, cumulative risks and burdens of repeat infection increased according to the number of infections. Limitations included a cohort of mostly white males. The evidence shows that reinfection further increases risks of death, hospitalization and sequelae in multiple organ systems in the acute and postacute phase. Reducing overall burden of death and disease due to SARS-CoV-2 will require strategies for reinfection prevention.

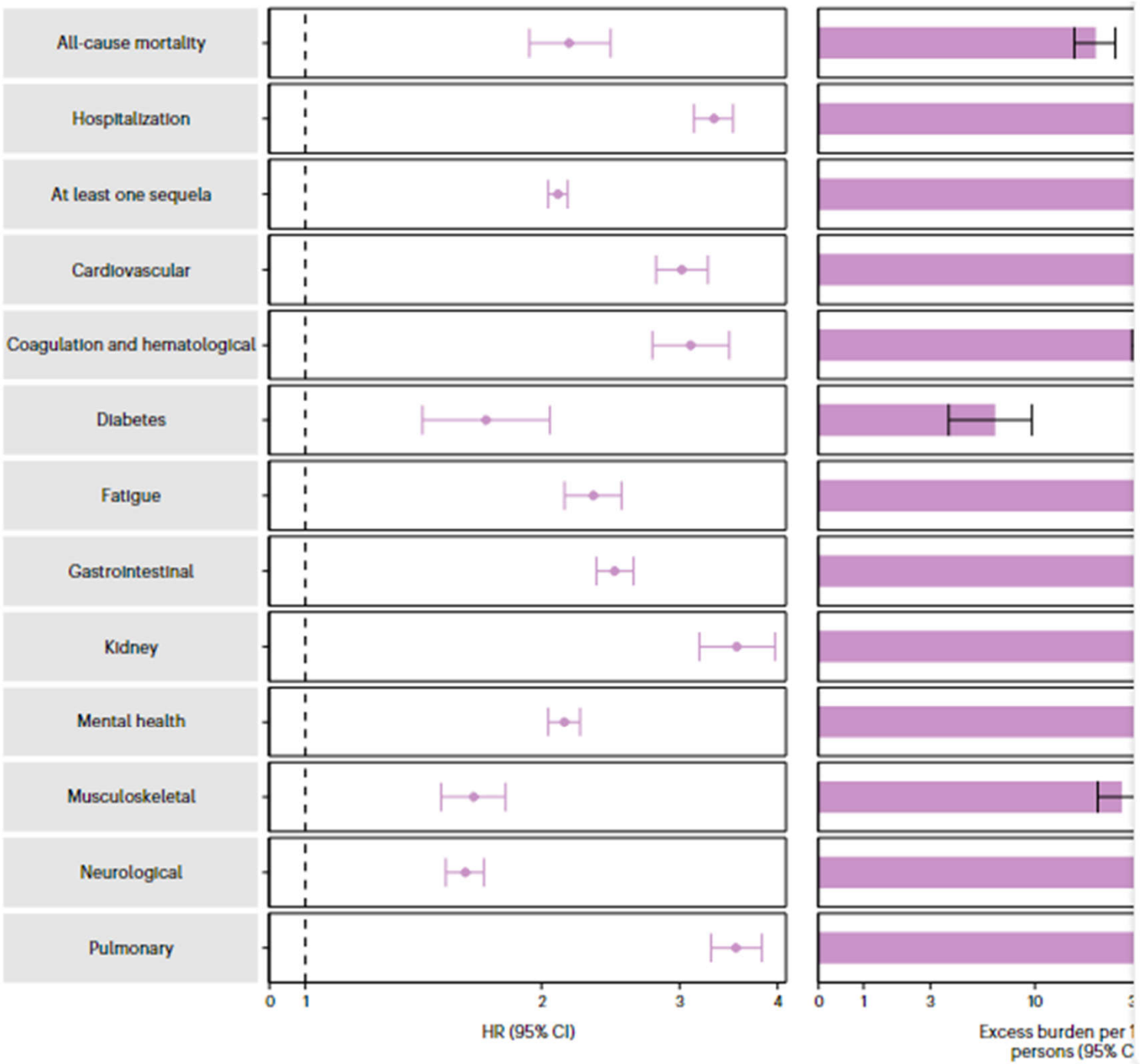

Fig. 1 | Risk and burden of sequelae in people with SARS-CoV-2 reinfection ($n = 443,588$) are compared. Adjusted HRs (dots) and 95%

COMMENTARY

THE AMERICAN JOURNAL of MEDICINE®

Using SARS-CoV-2 Antibody Testing in COVID-19 Research

SEE RELATED ARTICLE, p 568.

The novel coronavirus disease 2019 (COVID-19) pandemic is the first communicable disease in almost a century to surpass chronic and noncommunicable diseases as the leading cause of death and morbidity worldwide.[1] Such unprecedented deep and widespread impact of an infectious disease in the modern era, which boasts of state-of-the-art medical accomplishments, is alarming and yet intriguing.

In the current issue, Ma et al[2] have investigated the association between physical activity and COVID-19 severity risks by identifying prior severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection as either self-reported or by presence of antibodies. There is a fundamental vulnerability in utilizing antibodies to determine proof gaps on this topic 3 years into the pandemic. Reverse transcription polymerase chain reaction (RT-PCR) remains a gold standard for the diagnosis of current infection. However, there lacks a consensus in the scientific and medical community on whether prior infections can be accurately identified either by leveraging current biomedical techniques or by development of innovative ones.

There are 4 structural proteins encoded by the SARS-CoV-2 genome, of which 2 are of high interest in determining antibody reactivity—membrane glycoprotein Spike (S) and nucleocapsid (N).[5] S-protein is the surface protein primarily involved in binding to host cells, whereas N-protein is involved in penetrating the host's nucleus and promoting virus replication. Historically, S-protein specific immunoglobulin (Ig; IgG, IgA, or IgM) antibody measurement has been the mainstay of assessing SARS-CoV-2 immunologi-

major pitfalls to this approach.

First, seroreversion (waning or loss of antibody detectability) occurs in all individuals and is not uniformly distributed over time. Post infection, antibody levels significantly decrease by ~6 months and may even become undetectable in many cases. Longitudinal scientific data from multiple clinical trials and observational studies, which has been incorporated by the Centers for Disease Control and Prevention and the US Food and Drug Administration, have determined that postvaccination antibody levels wane significantly by ~8-10 months. These findings are the *principalis causa* for regular booster doses. Therefore, the mere absence of S- or N-antibodies is a nonreliable metric to determine "no prior infection/vaccination." Second, not all individuals produce a sufficient antibody response to infection or vaccination (seroconversion). In fact, individuals with pre-existing chronic health conditions have a multifold higher likelihood of being seronegative (absence of Spike IgG) even after completing full vaccination regimen.[9] Third, seroconversion timeline is not uniform across all individuals. Although public health guidelines recommend a minimum 14-day incubation period after final vaccination dose or infection diagnosis for developing measurable antibody levels, there are multiple reports of individuals seroconverting well after that timeframe. Fourth, seroreactivity will differ among different variants given the varying number of mutations on Spike protein (eg, delta and omicron), which could potentially affect seroconversion lag time. Moreover, we also need to consider whether IgM or IgA (S or N specific) can provide material, and involves a considerable amount of time. Although seropositive status is positively correlated with microneutralization and plaque reduction neutralization assays, serology is unable to describe the full effect-size of the immune response, which may be important indices of COVID-19 research.[12] As mentioned above, the strength of neutralizing titers as actual correlate of protection remains to be established. Additionally, with the surge of highly contagious variants and their subvariants, virology experts are currently studying the feasibility and utility of serology and monoclonal antibody reagents to determine the degree of actual immunity (protection). Any such breakthrough will have to be detailed yet broad based, and obviously, must stand the test of time.

In conclusion, SARS-CoV-2 antibody measurements are powerful and informative tools with some glaring limitations. Clinical RT-PCR confirmation or self-reported disease are clearly necessary to augment the meaningful use of any SARS-CoV-2 antibody data. Secondary analysis of large registry data need to incorporate models with deeper appreciation of the complex yet important immune response. Only then can we move the needle toward accurate interpretation and dissemination of antibody results in COVID-19 research. Vaccination saves lives!

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THE END