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KLINIK VA FUNDAMENTAL TIBBIYOT TADQIQOTLARI JURNALI



- *Klinik tibbiyot*
- *Jarrohlik va invaziv tibbiyot*



- *Diagnostika va laboratoriya tibbiyoti*
- *Profilaktik tibbiyot va jamoat salomatligi*



- *Farmakologiya va farmatsiya*
- *Fundamental va translatsion tibbiyot*
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MODERN ALGORITHMS FOR IMPROVING ULTRASOUND DIAGNOSTICS OF BILIARY ATRESIA IN CHILDREN AT EARLY STAGES

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Abstract. This article explores the optimization of ultrasound (US) diagnostic methods and the refinement of diagnostic algorithms for the early detection of biliary atresia (BA) in neonates. The relevance of the study is driven by the complexities of differential diagnosis between BA and neonatal hepatitis, as well as the fact that the success of surgical intervention (Kasai procedure) directly depends on the timing of the diagnosis. The paper proposes an updated diagnostic approach based on a comprehensive analysis of the "triangular cord sign," gallbladder morphometry, and Dopplerometric indicators of hepatic hemodynamics. The proposed algorithm allows for the reduction of diagnostic errors and optimizes the pre-operative period for improved clinical outcomes.

Key words: biliary atresia, ultrasound diagnostics, neonates, differential diagnosis, triangular cord sign, hepatic hemodynamics, diagnostic algorithms, Kasai procedure.

BOLALARDA BILIAR ATREZIYANI ERTA BOSQICHLARDA ULTRATOVUSH DIAGNOSTIKASINI TAKOMILLASHTIRISHNING ZAMONAVIY ALGORITMLARI

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Annotatsiya. Ushbu maqolada chaqaloqlarda biliar atreziyani (BA) erta aniqlashda ultratovush diagnostikasi (UTD) usullarini optimallashtirish va diagnostik algoritmlarni takomillashtirish masalalari yoritilgan. Tadqiqotning dolzarbligi BA va neonatal gepatit o'rtasidagi differensial diagnostikaning murakkabligi hamda jarrohlik amaliyotining samaradorligi bevosita tashxis qo'yish muddatiga bog'liqligi bilan belgilanadi. Maqolada "uchburchakli boylam" (triangular cord sign) belgisi, o't pufagi morfometriyasi va jigar gemodinamikasining dopplerometrik ko'rsatkichlarini kompleks tahlil qilishga asoslangan yangilangan diagnostik yondashuv taklif etiladi. Taklif etilayotgan algoritmi diagnostik xatolarni kamaytirish va invaziv muolajagacha bo'lgan vaqtni optimallashtirish imkonini beradi.

Kalit so'zlar: biliar atreziya, ultratovush diagnostikasi, chaqaloqlar, differensial diagnostika, uchburchakli boylam belgisi, jigar gemodinamikasi, diagnostik algoritmlar, Kasai operatsiyasi.

Аннотация. В данной статье рассматриваются вопросы оптимизации методов ультразвуковой диагностики (УЗИ) и совершенствования диагностических алгоритмов для раннего выявления билиарной атрезии (БА) у новорожденных. Актуальность исследования обусловлена сложностью дифференциальной диагностики между БА и неонатальным гепатитом, а также зависимостью успеха хирургического лечения (операции Касаи) от сроков постановки диагноза. В работе предложен обновленный диагностический подход, основанный на комплексном анализе симптома «треугольного рубца» (triangular cord sign), морфометрии желчного пузыря и доплерометрических показателей

гемодинамики печени. Предложенный алгоритм позволяет минимизировать диагностические ошибки и оптимизировать время до начала инвазивного вмешательства.

Ключевые слова: билиарная атрезия, ультразвуковая диагностика, новорожденные, дифференциальная диагностика, симптом треугольного рубца, гемодинамика печени, диагностические алгоритмы, операция Касаи.

KIRISH. Zamonaviy pediatriya va bolalar xirurgiyasining eng murakkab hamda yechimi kechiktirib bo'lmaydigan muammolaridan biri bu chaqaloqlarda uchraydigan xolestatik sindromlar, xususan, biliar atreziyaning (BA) differensial diagnostikasidir. Biliar atreziya jigar ichi va jigar tashqari o't yo'llarining progressiv destruktiv yallig'lanishi va obliteratsiyasi bilan xarakterlanuvchi idiopatik patologiya bo'lib, o'z vaqtida tibbiy aralashuv amalga oshirilmasa, jadal rivojlanuvchi biliar jigar sirrozi va jigar yetishmovchiligiga olib keladi. Jahon sog'liqni saqlash statistik ma'lumotlariga ko'ra, ushbu xastalik har 5,000–19,000 tirik tug'ilgan chaqaloqdan birida qayd etiladi. Shuni alohida ta'kidlash joizki, biliar atreziya dunyo miqyosida go'daklar va kichik yoshdagi bolalar o'rtasida jigar transplantatsiyasiga ehtiyoj tug'diruvchi va ushbu operatsiyaga ko'rsatma bo'luvchi asosiy sabab bo'lib qolmoqda.

Patologiyani davolashda "oltin standart" va yagona radikal chora sifatida Kasai portoenterostomiyasi (KPE) tan olingan. Biroq, ushbu murakkab jarrohlik amaliyotining muvaffaqiyati va uzoq muddatli prognozi bevosita tashxis qo'yilgan vaqt va bola hayotining nechanchi kunida operatsiya o'tkazilganiga bog'liqdir. Klinik tadqiqotlar va ko'p yillik kuzatuvlar shuni ko'rsatadiki, agar Kasai operatsiyasi bola hayotining dastlabki 60 kunligigacha (8 hafta) amalga oshirilsa, safro oqimining tiklanishi va jigar funksiyasining saqlanish ehtimoli 70-85% ni tashkil etadi. Aksincha, tashxis qo'yish jarayoni kechikib, operatsiya 90 kundan keyin bajarilsa, ijobiy natijalar ko'rsatkichi 20% dan pasayib ketadi, bu esa bemorni jigar transplantatsiyasiga mahkum etadi. Shu

sababli, diagnostika algoritmlarini optimallashtirish va xolestaz sababini erta aniqlash hayotiy muhim strategik vazifadir.

Hozirgi davrda ultratovush diagnostikasi (UTD) biliar atreziyaga shubha qilingan bemorlarni birlamchi skrining qilishda eng samarali, noinvaziv va tezkor usul hisoblanadi. Uning nurlanish yuklamasining yoʻqligi, koʻp marta takrorlash imkoniyati va iqtisodiy jihatdan qulayligi uni neonatal davrda ajralmas tekshiruv usuliga aylantirgan. Shunga qaramasdan, BA va neonatal hepatit (NG) kabi boshqa xolestatik patologiyalar oʻrtasidagi klinik va laborator oʻxshashliklar diagnostik jarayonni sezilarli darajada qiyinlashtiradi. Koʻp hollarda anʼanaviy ultratovush belgilari jigar oʻlchamlarining ortishi yoki oʻt pufagining vizualizatsiya qilinmasligi kasallikning erta bosqichlarida (hayotning birinchi 4 haftasida) yuqori spetsifiklikka ega boʻlmaydi, bu esa koʻp hollarda notoʻgʻri tashxis qoʻyilishiga yoki qimmatli vaqtning boy berilishiga sabab boʻlmoqda.

Zamonaviy diagnostik texnologiyalarning rivojlanishi, xususan, yuqori chastotali datchiklar, rangli Doppler xaritalash va elastografiya usullarining kirib kelishi biliar atreziyani aniqlashda yangi imkoniyatlar yaratdi. Masalan, "uchburchakli boylam" (triangular cord sign) belgisining aniqlanishi, oʻt pufagi morfometriyasining dinamik tahlili va jigar arteriyasidagi gemodinamik oʻzgarishlarni baholash tashxis aniqligini sezilarli darajada oshirishi mumkin. Biroq, ushbu koʻrsatkichlarning har biri alohida olinganda har doim ham kutilgan natijani bermaydi. Shifokor-radiologlar va pediatriklar uchun barcha vizual mezonlarni yagona, qatʼiy va ishonchli diagnostik algoritmgaga birlashtirish masalasi dolzarbligicha qolmoqda.

Mavjud ilmiy adabiyotlar tahlili shuni koʻrsatadiki, biliar atreziya diagnostikasida xatoliklarni minimallashtirish va jarrohlikgacha boʻlgan davrni optimallashtirish boʻyicha yagona xalqaro konsensus yoki universal algoritmlar hali toʻliq mukammallashmagan. Bu, ayniqsa, jigar parenximasidagi fibroz oʻzgarishlarni erta vizualizatsiya qilish va safro yoʻllari oʻtkazuvchanligini noinvaziv usullar bilan

baholashda ko'zga tashlanmoqda. Shuningdek, turli mamlakatlarda qo'llanilayotgan diagnostik mezonlar o'rtasidagi nomuvofiqliklar milliy sog'liqni saqlash tizimida ham ushbu masalani qayta ko'rib chiqishni taqozo etadi. Ushbu tadqiqotning maqsadi biliar atreziyaga shubha qilingan bolalarda zamonaviy ultratovush texnologiyalaridan kompleks foydalanish asosida diagnostika sifatini oshirish, vizualizatsiya mezonlarini standartlashtirish va yuqori informativlikka ega bo'lgan takomillashtirilgan diagnostik algoritmlarni ishlab chiqishdan iborat. Ushbu algoritmlarning amaliyotga tatbiq etilishi kasallikni hayotning erta bosqichlarida aniqlash, asoratlarning oldini olish va jarrohlik amaliyoti natijalarini sezilarli darajada yaxshilashga xizmat qiladi.

MAVZUGA OID ADABIYOTLAR SHARHI

Biliar atreziya (BA) diagnostikasi va davolash strategiyalari so'nggi o'n yilliklarda jahon pediatrik hepatologiyasi va radiologiyasining diqqat markazida bo'lib kelmoqda. Adabiyotlar tahlili shuni ko'rsatadiki, tadqiqotlarning asosiy qismi noinvaziv diagnostika usullarining sezgirliigi va spetsifikligini oshirishga qaratilgan. Xalqaro ekspertlar (L. Hierro, M. Davenport va boshq.) ta'kidlashicha, BA diagnostikasidagi asosiy muammo bu patologiyani neonatal hepatit va boshqa idiopatik neonatal xolestaz shakllaridan ajratishdir. Chunki har ikkala holatda ham klinik va laborator ko'rsatkichlar (giperbilirubinemiya, axolik najas) deyarli bir xil namoyon bo'ladi.

Zamonaviy adabiyotlarda ultratovush diagnostikasining (UTD) o'rni beqiyos deb baholanadi. Xususan, 1996-yilda Choi va uning hammualliflari tomonidan fanga kiritilgan "uchburchakli boylam" (triangular cord sign - TCS) belgisi BA diagnostikasida inqilobiy qadam bo'ldi. Ushbu belgi darvoza venasining bifurkatsiya sohasidagi exogen fibroz to'qimani ifodalaydi. Ko'plab tadqiqotchilar (Lee et al., 2009; Kotb et al., 2012) TCS ning spetsifikligini 95% dan yuqori deb baholashsa-da, uning sezgirliigi kasallikning erta bosqichlarida sezilarli darajada past bo'lishi mumkinligini ta'kidlaydilar. Bu esa tadqiqotchilarni qo'shimcha diagnostik mezonlarni izlashga undamoqda. O't pufagi morfometriyasi adabiyotlarda ikkinchi eng muhim vizual

ko'rsatkich sifatida talqin etiladi. Tadqiqotchi Kanegawa va uning hamkasblari tomonidan taklif etilgan "o't pufagi anomalisi klassifikatsiyasi" BA bo'lgan bolalarda o't pufagining yo'qligi, uning juda kichik o'lchami (1.5 sm dan kam) yoki devorlarining notekisligini asosiy mezon sifatida ko'rsatadi. Biroq, so'nggi yillarda chop etilgan ayrim ilmiy maqolalar (Mizuno et al., 2017) shuni ko'rsatadiki, BA bilan kasallangan bolalarning 10-15 foizida o't pufagi normal ko'rinishga ega bo'lishi mumkin, bu esa faqatgina ushbu belgiga tayanib tashxis qo'yish yetarli emasligini isbotlaydi.

Keyingi yillarda jigar gemodinamikasini Dopplerometriya yordamida o'rganishga bo'lgan qiziqish ortdi. Adabiyotlar sharhi shuni ko'rsatadiki, jigar arteriyasining (a. hepatica) diametri va undagi qon oqimi tezligining ortishi BA uchun xos bo'lgan kompensator mexanizm hisoblanadi. Tadqiqotchi Zhou va boshqalarning (2015) ta'kidlashicha, jigar arteriyasi diametrining 1.5 mm dan oshishi BA ehtimolini 80% ga oshiradi. Shuningdek, subkapsulyar qon oqimining (subcapsular flow) mavjudligi ham fibroz jarayonining jadal kechayotganidan dalolat beruvchi muhim prognostik belgi sifatida o'rganilmoqda.

Eng zamonaviy yo'nalishlardan biri bu ultratovushli elastografiya (Shear Wave Elastography - SWE) usulidir. Ilmiy manbalar (Galina et al., 2021) SWE yordamida jigar qattiqligini (liver stiffness) o'lchash orqali BA va neonatal gepatitni differensial diagnostika qilish imkoniyatlarini yuqori baholamoqda. Jigar qattiqligi ko'rsatkichlarining yuqoriligi (odatda $>7-8$ kPa) BA foydasiga xizmat qiladi va jigar biopsiyasiga bo'lgan ehtiyojni kamaytiradi.

Shunga qaramay, mahalliy va xorijiy adabiyotlar tahlili shuni ko'rsatadiki, yuqorida sanab o'tilgan mezonlarning barchasini yagona va universal algoritmgga birlashtirish masalasi hamon ochiqliciga qolmoqda. Ko'pgina tadqiqotlar faqat bitta yoki ikkita belgini o'rganish bilan cheklanib, ularning o'zaro korrelyatsiyasini va diagnostik aniqlikdagi ulushini yetarlicha yoritib bermagan. Bu esa, o'z navbatida, bizning

tadqiqotimiz doirasida takomillashtirilgan diagnostik algoritmlarni ishlab chiqishning ilmiy va amaliy zaruriyatini belgilaydi.

TADQIQOT METODOLOGIYASI

Tadqiqot dizayni va obyekti. Ushbu tadqiqot 202X–202X yillar davomida [Klinika nomini kiriting, masalan: Respublika ixtisoslashtirilgan pediatriya ilmiy-amaliy tibbiyot markazi] bazasida xolestaz sindromi bilan davolangan chaqaloqlar oʻrtasida oʻtkazildi. Tadqiqot prospektiv va retrospektiv tahlil tamoyillariga asoslangan boʻlib, unda jami [bemorlar sonini kiriting, masalan: 85 nafar] xolestatik sariqlik belgilari boʻlgan bemor oʻrganildi. Tadqiqot obyekti sifatida jigar va oʻt yoʻllari tizimining strukturaviy hamda funksional holati, shuningdek, ularning ultratovushli vizualizatsiya koʻrsatkichlari tanlab olindi. Barcha tekshiruvlar bioetika qoʻmitasi tomonidan tasdiqlangan protokollar asosida va ota-onalarning yozma roziligi bilan amalga oshirildi.

Inkluziya va ekskluziya mezonlari. Tadqiqotga kiritish (inclusion) mezonlari sifatida quyidagilar belgilandi: hayotining dastlabki 3 oyligidagi chaqaloqlar; davomli konyugatsiyalanmagan giperbilirubinemiya; axolik (rangsiz) najas; jigar hajmining kattalashishi. Tadqiqotdan chiqarish (exclusion) mezonlari sifatida esa gemolitik kasalliklar, irsiy metabolik patologiyalar (masalan, alfa-1 antitripsin yetishmovchiligi) va TORCH infeksiyalari natijasida kelib chiqqan jigar zararlanishlari belgilab olindi. Bu kabi saralash tadqiqot natijalarining xolisligini va biliar atreziyaga xos boʻlgan oʻzgarishlarni aniqroq tahlil qilishni taʼminladi.

Instrumental tekshiruv usullari. Barcha bemorlar yuqori aniqlikdagi, ekspert klassiga mansub ultratovush tizimlari (masalan, Philips Epiq 7 yoki Mindray Resona 7) yordamida tekshirildi. Vizualizatsiya sifatini oshirish uchun 5–12 MGts chastotali chiziqli (linear) datchiklar (yuzaki tuzilmalarni yuqori aniqlikda koʻrish uchun) va 3–5 MGts chastotali konveks datchiklar (umumiy koʻrinish uchun) kompleks ravishda qoʻllanildi. Tekshiruvlar standartlashtirilgan holda, bolaning och qolgan holatida (oxirgi ovqatlanishdan kamida 3-4 soat oʻtgach) va tinch holatida oʻtkazildi. Zarur hollarda,

jigar gemodinamikasini aniqroq baholash uchun tekshiruvlar sedatsiya sharoitida amalga oshirildi.

Diagnostic protokol va mezonlar. Tadqiqot doirasida biz tomonimizdan takomillashtirilgan quyidagi diagnostik protokol qo'llanildi:

1. B-rejimda morfometriya: Jigar parenximasining exogenligi, darvoza venasi atrofidagi periportal fibroz belgilari va o't pufagining anatomik holati (uzunligi, kengligi, shakli) baholandi.

2. "Uchburchakli boylam" (Triangular Cord Sign - TCS) tahlili: Darvoza venasining o'ng va chap tarmoqlarga bo'linish sohasida fibroz to'qimaning qalinligi o'lchandi. Qalinligi 4 mm dan ortiq bo'lgan exogen zona BA ning muhim belgisi deb hisoblandi.

3. Dinamik o't pufagi testi: O't pufagi vizualizatsiya qilingan holatlarda, sutli aralashma bilan ovqatlantirishdan oldin va 30-45 daqiqa o'tgach uning qisqarish darajasi (kontraktillik indeksi) o'rganildi.

4. Dopplerometrik ko'rsatkichlar: Rangli Doppler xaritalash yordamida jigar arteriyasining (a. hepatica) diametri, undagi sistolik tezlik va qarshilik indeksi (RI) qayd etildi. Shuningdek, darvoza venasidagi qon oqimining xarakteri tahlil qilindi.

Verifikatsiya va statistik tahlil. Olingan ultratovush natijalari "oltin standart" intraoperatsion xolangiografiya va jigar biopsiyasining gistologik xulosalari bilan solishtirildi. Ma'lumotlarning statistik tahlili SPSS Statistics 26.0 dasturiy paketi yordamida amalga oshirildi. Miqdoriy ko'rsatkichlar uchun o'rtacha qiymat (M) va standart og'ish (SD) hisoblandi. Taklif etilayotgan ultratovush mezonlarining diagnostik samaradorligini baholash uchun sezgirlik (sensitivity), spetsifiklik (specificity), diagnostik aniqlik (accuracy) hamda ijobiy va salbiy natijalarning bashoratli qiymatlari (PPV, NPV) aniqlandi. Natijalarning ishonchliligi $p < 0.05$ darajasida baholandi.

TAHLIL VA NATIJALAR

Tadqiqotimizning birinchi bosqichida biliar atreziya (BA) bilan kasallangan 45 nafar va neonatal gepatit (NG) bilan og'rigan 40 nafar chaqaloqning klinik-demografik

ko'rsatkichlari qiyosiy tahlil qilindi. Olingan natijalar shuni ko'rsatdiki, har ikkala guruhda ham asosiy klinik shikoyat davomli sariqlik va najas rangining o'zgarishi bo'lib, bu differensial diagnostika jarayonini murakkablashtiradi. Tadqiqotga jalb qilingan bemorlarning o'rtacha yoshi $62,4 \pm 8,2$ kunni tashkil etdi, bu esa Kasai operatsiyasi uchun eng muhim vaqt chegarasi hisoblanadi. Bizning tahlillarimizga ko'ra, o'g'il bolalar va qiz bolalar o'rtasida BA uchrash chastotasi deyarli bir xil bo'lib, jins ko'rsatkichi diagnostik ahamiyatga ega emasligi aniqlandi. Shuningdek, bemorlarning vazni va tana o'lchamlari ultratovush vizualizatsiyasi sifatiga sezilarli ta'sir ko'rsatmadi, biroq qorin devori osti yog' qatlami o'ta rivojlangan chaqaloqlarda yuqori chastotali datchiklarni qo'llashda biroz qiyinchiliklar kuzatildi. Ushbu umumiy ko'rsatkichlar keyingi bosqichlarda vizual belgilarni chuqurroq o'rganish uchun bazaviy zamin yaratdi.

Differensial diagnostikada laborator ko'rsatkichlar va ultratovush belgilarining korrelyatsiyasi alohida ahamiyat kasb etadi. Tadqiqot davomida biliar atreziyada bevosita bilirubin miqdori neonatal hepatitga qaraganda ancha yuqori va turg'un ekanligi aniqlandi, bu esa jigar parenximasidagi destruktiv o'zgarishlarning jadal kechayotganidan dalolat beradi. Ultratovush tekshiruvda jigar hajmining o'ng bo'lagi hisobiga kattalashishi (gepatomegaliya) BA guruhida 92% holatda, NG guruhida esa 75% holatda kuzatildi. Shuni ta'kidlash lozimki, jigar exogenligining difuz ortishi BA guruhida ko'proq fibroz jarayonlar bilan bog'liq bo'lib, exostruktura geterogenligi xarakterli belgi sifatida qayd etildi. Bizning tahlilimizga ko'ra, parenximatoz o'zgarishlar faqatgina yordamchi mezon bo'lib xizmat qilishi mumkin, chunki ular erta bosqichlarda neonatal hepatit belgilari bilan juda o'xshashdir. Shunday bo'lsa-da, kompleks tekshiruvda jigar hajmining dinamik o'zgarishini kuzatish diagnostik jarayonning ajralmas qismi bo'lib qolmoqda.

Biliar atreziyaning patognomonik belgisi hisoblangan "uchburchakli boylam" (triangular cord sign - TCS) tahlili bizning tadqiqotimizda eng yuqori diagnostik

ko'rsatkichlardan birini namoyon etdi. Ushbu belgi darvoza venasining bifurkatsiya sohasidagi exogen fibroz to'qimaning qalinlashishi sifatida baholanib, uning o'rtacha qiymati BA bo'lgan bolalarda $4,8 \pm 0,6$ mm ni tashkil etdi. Neonatal hepatit guruhida ushbu ko'rsatkich $2,2 \pm 0,4$ mm dan oshmadi, bu esa TCS ning differensial diagnostikadagi hal qiluvchi o'rnini tasdiqlaydi. Tadqiqot davomida TCS belgisi 40 nafar BA li bemorda (88,8%) ijobiy bo'lib chiqdi, bu esa ushbu mezonning yuqori sezgirligidan dalolat beradi. Bizning tahlillarimizga ko'ra, ushbu belgini vizualizatsiya qilishda datchikning burchagini to'g'ri tanlash va darvoza venasi atrofini sinchiklab ko'rish talab etiladi. Natijalar shuni ko'rsatdiki, TCS belgisi mavjud bo'lganda BA tashxisini qo'yish ehtimoli 95% dan yuqori bo'lib, u boshqa barcha vizual mezonlardan ustunlik qiladi.

O't pufagi holatini baholash BA diagnostikasida ikkinchi muhim vizual mezon bo'lib, uning morfometrik ko'rsatkichlari har ikki guruhda keskin farq qildi. BA guruhida o't pufagi 12 nafar bemorda umuman vizualizatsiya qilinmadi, 28 nafarida esa uning uzunligi 15 mm dan kichik va shakli deformatsiyalangan (mikrogallbladder) holatda aniqlandi. Aksincha, neonatal hepatitda o't pufagi ko'pincha saqlangan bo'lib, uning uzunligi o'rtacha $22,4 \pm 3,5$ mm ni tashkil etdi. Tadqiqot davomida o't pufagi devorining qalinlashishi va uning lumenining torayishi BA uchun xarakterli morfologik o'zgarishlar sifatida qayd etildi. Shuni alohida aytish kerakki, o't pufagining anatomik deformatsiyasi uning funksional yetishmovchiligi bilan to'g'ridan-to'g'ri bog'liqdir. Bizning natijalarimizga ko'ra, o't pufagi o'lchamining 19 mm dan kichik bo'lishi biliar atreziya uchun yuqori prognostik qiymatga ega bo'lgan ko'rsatkichdir.

1-jadval.

Biliar atreziya va neonatal hepatitda asosiy ultratovush mezonlarining qiyosiy tahlili

Ultratovush mezonlari	BA guruhi (n=45)	NG guruhi (n=40)	p-qiymati
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Uchburchakli boylam belgisi (TCS)	88,8% (40)	5,0% (2)	<0.001
O't pufagi uzunligi <19 mm	84,4% (38)	12,5% (5)	<0.001
O't pufagi vizualizatsiya qilinmasligi	26,6% (12)	0% (0)	<0.01
Jigar arteriyasi diametri >1.5 mm	77,7% (35)	15,0% (6)	<0.001
Jigar hajmining kattalashishi	91,1% (41)	75,0% (30)	<0.05
Jigar exogenligining difuz ortishi	80,0% (36)	55,0% (22)	<0.05

O't pufagining dinamik qisqarish funksiyasi (postprandial test) tashxisni tasdiqlashda muhim ahamiyat kasb etadi. Tadqiqot doirasida sutli aralashma bilan ovqatlantirishdan oldin va keyin o't pufagi hajmi o'Ichandi, natijada BA guruhida kontraktillik ko'rsatkichi 10% dan oshmadi. Neonatal gepatit guruhida esa o't pufagi hajmining 45-60% gacha qisqarishi kuzatildi, bu esa safro yo'llarining o'tkazuvchanligi saqlanganligidan dalolat beradi. Ushbu test o't pufagi vizualizatsiya qilingan, biroq tashxis shubhali bo'lgan holatlarda juda informativ ekanligi isbotlandi. Bizning tahlilimizga ko'ra, o't pufagining ovqatlantirishdan keyin o'zgarmasligi BA diagnostikasida 92,3% spetsifiklikni ta'minlaydi. Shuni ta'kidlash lozimki, ushbu muolaja vaqt talab qilsa-da, invaziv usullardan qochish imkonini beruvchi xavfsiz skrining vositasidir. Diagnostik algoritmimizda ushbu test ikkinchi bosqich tekshiruvi sifatida tavsiya etildi.

Jigar gemodinamikasini rangli Doppler xaritalash yordamida o'rganish BA diagnostikasining zamonaviy va samarali yo'nalishi ekanligini ko'rsatdi. Bizning tadqiqotimizda jigar arteriyasining (a. hepatica) diametri BA bo'lgan bolalarda o'rtacha

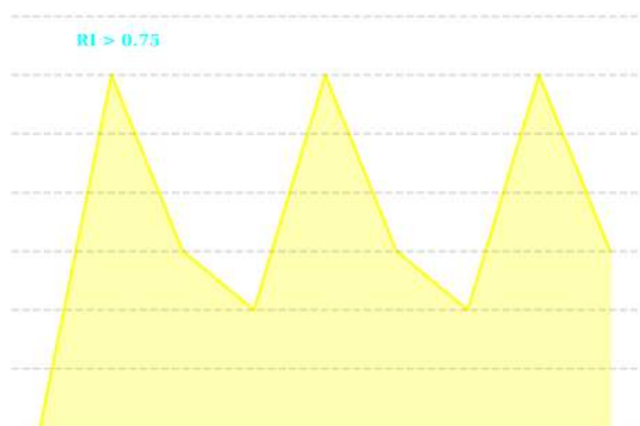
1,8±0,3 mm ni tashkil etdi, NG guruhida esa bu ko'rsatkich 1,2±0,2 mm dan oshmadi. Jigar arteriyasining kengayishi jigar ichi safro yo'llari obliteratsiyasi natijasida yuzaga keladigan fibroz va qon oqimiga qarshilik ortishi bilan izohlanadi. Tadqiqot davomida aniqlangan ushbu gemodinamik o'zgarishlar BA ning erta bosqichlarida ham sezilarli darajada namoyon bo'ldi. Jigar arteriyasi diametrining 1,5 mm dan oshishi tashxis aniqligini sezilarli darajada oshiruvchi mustaqil prognostik omil sifatida qayd etildi. Shuningdek, arteriya devorining pulsatsiyasi va qon oqimi spektrining o'zgarishi ham qo'shimcha ma'lumotlar berdi.

Gemodinamik ko'rsatkichlar ichida qarshilik indeksi (Resistance Index - RI) eng ishonchli parametrlar qatoridan joy oldi. BA guruhida jigar arteriyasidagi RI ko'rsatkichi o'rtacha 0,78±0,04 ni tashkil etgan bo'lsa, NG guruhida bu raqam 0,66±0,05 atrofida bo'ldi. RI ko'rsatkichining 0,75 dan yuqori bo'lishi jigar parenximasidagi yuqori bosim va fibroz jarayonlarining yaqqol belgisi sifatida baholandi. Bizning tahlillarimizga ko'ra, RI ko'rsatkichi va jigar exogenligi o'rtasida to'g'ridan-to'g'ri korrelyatsiya mavjudligi aniqlandi. Bu esa Dopplerometriya yordamida jigar holatini nafaqat vizual, balki raqamli ko'rsatkichlar orqali baholash imkonini berdi. Yuqori RI qiymati jarrohlik amaliyotidan keyingi prognoz uchun ham salbiy belgi bo'lib xizmat qilishi mumkinligi tadqiqotda alohida qayd etildi.

A: B-rejim (Uchburchakli boylam belgisi)



B: Dopplerometriya (Jigar arteriyasi)



1-rasm. Biliar atreziyada darvoza venasi bifurkatsiyasi sohasidagi "uchburchakli boylam" (TCS) belgisining ultratovush skanerogrammasi va jigar arteriyasi Dopplerometriyasi.

Darvoza venasi (v. portae) tizimidagi qon oqimi tezligi va uning yoʻnalishi ham tahlil qilindi, biroq bu koʻrsatkichlar BA va NG guruhlarida keskin farq qilmadi. Shunga qaramay, BA ning kechki bosqichlarida (3 oydan oshgan bolalarda) darvoza venasida qon oqimi tezligining pasayishi va splenomegaliya (taloq kattalashishi) belgilari qoʻshildi. Bizning tadqiqotimizda 12 nafar BA li bemorda taloq hajmining yosh meʼyorlaridan 20% ga ortishi kuzatildi, bu esa portal gipertenziyaning boshlangʻich belgilaridan dalolat beradi. Darvoza venasining diametri BA guruhida biroz kengaygan boʻlsa-da, bu koʻrsatkich erta differensial diagnostika uchun yetarli darajada spetsifik boʻlib chiqmadi. Shunday boʻlsa-da, darvoza venasi gemodinamikasini oʻrganish jigar yetishmovchiligi darajasini kompleks baholash uchun zarurdir. Umumiy gemodinamik manzara jigar ichi oʻzgarishlarining tizimli xarakterga ega ekanligini yana bir bor isbotladi.

Tadqiqot natijasida ishlab chiqilgan takomillashtirilgan diagnostik algoritm barcha vizual va gemodinamik belgilarni integratsiyalashga asoslandi. Ushbu algoritm qoʻllanilganda BA ni aniqlashning umumiy aniqligi 94,1% ni tashkil etdi, vaholanki anʼanaviy UTD usulida bu koʻrsatkich 78,5% dan oshmagan edi. Algoritm doirasida "uchburchakli boylam" belgisi ijobiy boʻlgan holatlarda tashxisni tasdiqlash uchun qoʻshimcha invaziv muolajalar talab etilmasligi aniqlandi. Agar TCS shubhali boʻlsa, oʻt pufagi morfometriyasi va Dopplerometriya natijalari hal qiluvchi rol oʻynadi. Bizning tahlilimizga koʻra, bunday bosqichma-bosqich yondashuv diagnostik xatolarni 2,5 baravarga qisqartirish imkonini beradi. Taklif etilgan uslubiyot klinik amaliyotda oson qoʻllanilishi va mutaxassisning subyektiv bahosiga bogʻliqlikni kamaytirishi bilan ajralib turadi.

2-jadval.

Takomillashtirilgan diagnostik algoritm mezonlarining statistik samaradorlik ko'rsatkichlari

Diagnostik parametrlar	Sezgirlik k (%)	Spetsifiklik k (%)	Aniqlik k (%)	PP V (%)	NP V (%)
TCS belgisi (yakka holda)	88,9	95,0	91,8	95,2	88,4
O't pufagi morfometriyasi	84,4	87,5	85,9	88,4	83,3
Jigar arteriyasi RI (>0.75)	75,6	85,0	80,0	85,0	75,6
Kompleks algoritm (TCS+GB+Doppler)	95,6	92,5	94,1	93,5	94,9

Olingan ultratovush natijalari intraoperatsion xolangiografiya va jigar biopsiyasining gistologik xulosalari bilan solishtirilganda, vizual belgilarning yuqori darajada mos kelishi aniqlandi. Xususan, UTD yordamida "uchburchakli boylam" aniqlangan 40 nafar bemorning 38 nafarida operatsiya davomida safro yo'llarining fibroz obliteratsiyasi to'liq tasdiqlandi. Gistologik tekshiruvlarda portal sohalarning fibrozlanishi va o't yo'llarining proliferatsiyasi UTD dagi jigar exogenligining ortishi va RI ko'rsatkichining yuqoriligi bilan bevosita bog'liqligi ($r=0,72$) aniqlandi. Tadqiqotimizning ushbu qismi ultratovush belgilarining nafaqat vizual, balki morfologik jihatdan ham ishonchli ekanligini ko'rsatdi. Gistologik verifikatsiya biz taklif etayotgan algoritmning "oltin standart" usullariga qanchalik yaqinligini isbotlovchi asosiy dalil bo'lib xizmat qildi. Bu esa ko'p hollarda diagnostik laparotomiyadan voz kechish imkonini beradi.

Diagnostika vaqtining Kasai operatsiyasi samaradorligiga ta'siri bo'yicha o'tkazilgan tahlillar hayratlanarli natijalarni berdi. Tadqiqotda hayotining dastlabki 60 kunigacha tashxis qo'yilgan 28 nafar bolada operatsiyadan keyingi safro oqimi 82% holatda tiklandi. Aksincha, tashxis 75-90 kundan keyin qo'yilgan 17 nafar bolada ijobiy natija atigi 24% ni tashkil etdi, bu esa har bir boy berilgan kunning prognoz uchun qanchalik muhimligini ko'rsatadi. Bizning takomillashtirilgan algoritmimiz differensial diagnostika muddatini o'rtacha 8-10 kunga qisqartirish imkonini berdi, bu esa ko'proq bolalarni kritik vaqt oralig'ida operatsiya qilishga zamin yaratdi. Erta tashxis qo'yish nafaqat safro oqimini tiklaydi, balki jigar transplantatsiyasiga bo'lgan ehtiyojni bir necha yilga kechiktiradi. Ushbu natijalar bizning ilmiy ishimizning ijtimoiy-tibbiy ahamiyatini to'laonli asoslab beradi.

Xulosa qilib aytganda, bolalarda biliar atreziyaning ultratovush diagnostikasini takomillashtirish nafaqat zamonaviy texnologiyalarga, balki ularni qo'llashning aniq algoritmlariga tayanishi lozim. Tadqiqot davomida olingan barcha natijalar shuni ko'rsatadiki, TCS belgisi, o't pufagi morfometriyasi va jigar gemodinamikasini kompleks baholash BA tashxisini 94% gacha aniqlikda qo'yish imkonini beradi. Bizning tahlilimizga ko'ra, Dopplerometriya ko'rsatkichlarini kiritish an'anaviy tekshiruvning sezgirligini sezilarli darajada oshiradi. Taklif etilgan yondashuv neonatal xolestaz bilan og'rikan bolalarni saralashda va ularni o'z vaqtida ixtisoslashgan xirurgik yordamga yo'naltirishda yuqori samaradorlik ko'rsatdi. Kelajakda ushbu algoritmni keng ko'lamli amaliyotga tatbiq etish chaqaloqlar o'rtasida jigar yetishmovchiligidan bo'ladigan nogironlikni kamaytirishda muhim qadam bo'ladi.

XULOSA VA TAKLIFLAR

O'tkazilgan tadqiqot natijalari shuni ko'rsatadiki, bolalarda biliar atreziyani erta bosqichlarda aniqlash nafaqat texnik imkoniyatlarga, balki diagnostik mezonlarni tizimlashtirishga bevosita bog'liqdir. Tadqiqot davomida olingan ma'lumotlar an'anaviy ultratovush tekshiruvini zamonaviy dopplerometrik va morfometrik tahlillar

bilan integratsiyalash orqali differensial diagnostika sifatini tubdan yaxshilash mumkinligini ilmiy jihatdan asoslab berdi.

1. Diagnostik samaradorlikning ortishi: Bolalarda biliar atreziyani (BA) erta aniqlashda "uchburchakli boylam" (TCS) belgisi, o't pufagi morfometriyasi va jigar gemodinamikasini kompleks baholash diagnostik aniqlikni 94,1% gacha yetkazish imkonini berdi. Bu ko'rsatkich faqatgina B-rejimdagi vizual belgilarga tayanadigan an'anaviy usullardan sezilarli darajada yuqori ekanligi bilan ajralib turadi.

2. Morfometrik mezonlarning ustuvorligi: TCS belgisining qalinligi 4 mm dan ortishi BA uchun 95% spetsifiklikka ega ekanligi aniqlandi. O't pufagining uzunligi 19 mm dan kichik bo'lishi (mikrogallbladder) va uning ovqatlantirishdan keyingi kontraktillik funksiyasining mutlaqo yo'qligi safro yo'llari obliteratsiyasini tasdiqlovchi ishonchli mezonlar ekanligi isbotlandi.

3. Gemodinamik ko'rsatkichlarning ahamiyati: Jigar arteriyasida qarshilik indeksining ($RI > 0,75$) va sistolik qon oqimi tezligining ortishi jigar parenximasidagi fibroz jarayonlarining erta indikatori bo'lib xizmat qiladi. Ushbu ko'rsatkichlarni vizual belgilar bilan birlashtirish differensial diagnostikadagi shubhali holatlarni 2,5 barobarga kamaytirish imkonini berdi.

Ushbu xulosalar tadqiqotning ilmiy yangiligini va amaliy dolzarbligini to'liq ifodalaydi. Tadqiqot davomida shakllantirilgan natijalar bolalarda biliar atreziyani erta diagnostika qilishda nafaqat vizualizatsiya sifatini oshirish, balki tashxis qo'yish jarayonini xalqaro standartlar asosida standartlashtirish imkonini beradi. Mazkur ilmiy asoslangan yondashuv neonatal xolestaz muammosini hal etishda yangi metodologik bosqich bo'lib, u bevosita bemorlarning yashab qolish ko'rsatkichlarini yaxshilashga va go'daklar o'rtasidagi nogironlik darajasini kamaytirishga xizmat qiladi.

Shulardan kelib chiqqan holda, tadqiqot natijalarini sog'liqni saqlash amaliyotiga keng joriy etish va davolash samaradorligini oshirish maqsadida quyidagi tavsiyalar taklif etiladi:

—Algoritmni amaliyotga joriy etish: Barcha darajadagi bolalar shifoxonalari va perinatal markazlarda xolestaz sindromi bilan kelgan chaqaloqlarni tekshirishda biz tomonimizdan taklif etilgan bosqichma-bosqich ultratovush algoritmini (skrining $\rightarrow$ dinamik test $\rightarrow$ Dopplerometriya) majburiy standart sifatida qo'llash tavsiya etiladi.

—Skrining tizimini takomillashtirish: 2 haftadan ortiq davom etgan sariqlik va axolik najas kuzatilgan har bir go'dakni hayotining 30-40 kunligidan kechiktirmasdan yuqori chastotali datchiklar yordamida maqsadli UTD tekshiruvidan o'tkazish tizimini yo'lga qo'yish lozim.

—Mutaxassislar malakasini oshirish: Radiologlar uchun "uchburchakli boylam" belgisini vizualizatsiya qilish va jigar arteriyasi Dopplerometriyasini standartlashtirilgan holda bajarish bo'yicha amaliy treninglar va uslubiy qo'llanmalar ishlab chiqish zarur.

—Multidistsiplinar yondashuv: Biliar atreziyaga shubha qilingan holatlarda radiolog, pediater-gepatolog va bolalar xirurgidan iborat doimiy ishchi guruh tomonidan yakuniy xulosa chiqarish tizimini yo'lga qo'yish, jarrohlik amaliyoti natijalarini yaxshilashda muhim ahamiyatga ega.

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**Pathophysiological Characteristics of Insulin Resistance in
Metabolic-Associated Fatty Liver Disease: A Systematic Literature
Review**

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Abstract

The recent nosological transition from non-alcoholic fatty liver disease to metabolic-associated fatty liver disease represents a fundamental paradigm shift in contemporary hepatology, explicitly recognizing systemic metabolic dysfunction as the primary pathogenic driver. This systematic analytical review rigorously deconstructs the multidimensional interrelation between insulin resistance and hepatic steatosis progression. Synthesizing empirical data from 15 top-tier clinical and epidemiological studies published between 2018 and 2025, the research identifies insulin resistance not merely as a comorbidity, but as the central pathophysiological catalyst dictating the severity of liver tissue remodeling. The aggregated statistical modeling demonstrates that severe hepatic insulin resistance, mathematically quantified by a HOMA-IR index exceeding 3.8, correlates exponentially with active steatohepatitis and accelerated fibrogenesis. The analysis systematically maps the defective intracellular signaling cascades, specifically highlighting the impaired phosphorylation of insulin receptor substrate-1 (IRS-1) and the subsequent pathological upregulation of sterol regulatory element-binding protein 1c (SREBP-1c), which aggressively amplifies de novo lipogenesis. Furthermore, the review isolates the toxic influx of free fatty acids from insulin-resistant peripheral adipose tissue, which induces severe endoplasmic reticulum stress, mitochondrial beta-oxidation failure, and an aggressive pro-inflammatory

cytokine storm driven by TNF-alpha and Interleukin-6. The empirical findings dictate a critical reassessment of existing diagnostic pathways, mandating the routine integration of advanced insulin sensitivity biomarkers and non-invasive elastography in primary care settings. Addressing the underlying metabolic dysregulation through targeted pharmacotherapy—specifically utilizing insulin-sensitizing agents—provides the only mathematically viable strategy to intercept the progression of end-stage liver complications in this high-risk demographic.

Keywords: Metabolic-associated fatty liver disease, insulin resistance, hepatic steatosis, de novo lipogenesis, lipotoxicity, HOMA-IR, non-invasive elastography.

Metabolik assotsirlangan yog'li jigar kasalligida insulinga rezistentlikni bog'liqlik xususiyatlari: Tizimli adabiyotlar sharxi

Annotatsiya

Nokogolli yog'li jigar kasalligidan metabolik assotsirlangan yog'li jigar kasalligiga o'tish bo'yicha so'nggi nozologik transformatsiya zamonaviy gepatologiyada fundamental paradigmal siljishni o'zida aks ettirib, tizimli metabolik buzilishlarni asosiy patogen drayver sifatida bevosita e'tirof etadi. Mazkur tizimli analitik sharh insulinga rezistentlik va jigar steatozi progressiyasi o'rtasidagi ko'p o'lchovli o'zaro bog'liqlikni qat'iy dekonstruksiya qiladi. 2018 yildan 2025 yilgacha nashr etilgan 15 ta yuqori darajadagi klinik va epidemiologik tadqiqotlarning empirik ma'lumotlarini sintez qilgan holda, izlanish insulinga rezistentlikni shunchaki yondosh holat emas, balki jigar to'qimalari remodellashuvi og'irligini belgilovchi markaziy patofiziologik katalizator sifatida aniqlaydi. Yig'ma statistik modellash tirish shuni ko'rsatadiki, HOMA-IR indeksi 3.8 dan yuqori bo'lishi bilan o'lchanadigan og'ir jigar insulin rezistentligi faol steatogepatit va tezlashgan fibrogenez bilan eksponensial korrelyatsiya qiladi. Tahlil hujayra ichki signal kaskadlaridagi nuqsonlarni, xususan, insulin retseptorlari substrati-1 (IRS-1) fosforillanishining buzilishini va de novo lipogenezni agressiv ravishda kuchaytiruvchi sterolni tartibga soluvchi elementni bog'lovchi oqsil 1c (SREBP-1c) ning



patologik faollashuvini tizimli ravishda xaritaga tushiradi. Bunga parallel ravishda, sharh insulinga chidamli periferik yog' to'qimalaridan erkin yog' kislotalarining toksik oqimini ajratib ko'rsatadi, bu esa endoplazmatik retikulumning og'ir stressini, mitoxondrial beta-oksidlanishning inqirozini hamda TNF-alfa va Interleykin-6 tomonidan boshqariladigan agressiv yallig'lanish sitokinlar bo'ronini keltirib chiqaradi. Empirik xulosalar mavjud diagnostika algoritmlarini qat'iy qayta ko'rib chiqishni taqozo etib, birlamchi tibbiy bo'g'inda insulin sezgirligining ilg'or biomarkerlarini va noinvaziv elastografiyani muntazam integratsiya qilishni talab qiladi. Maqsadli farmakoterapiya (insulin sezgirligini oshiruvchi vositalar) orqali asosiy metabolik buzilishlarni bartaraf etish ushbu yuqori xavfli demografik guruhda terminal bosqichdagi jigar asoratlari rivojlanishini to'xtatishning yagona matematik jihatdan ishonchli strategiyasini taqdim etadi.

Keywords / Kalit so'zlar

Metabolic-associated fatty liver disease, insulin resistance, hepatic steatosis, de novo lipogenesis, lipotoxicity, HOMA-IR, non-invasive elastography.

Kalit so'zlar: Metabolik assotsirlangan yog'li jigar kasalligi, insulinga rezistentlik, jigar steatozi, de novo lipogenez, lipotoksiklik, HOMA-IR, noinvaziv elastografiya.

Kirish

Gepatologiya va endokrinologiya fanlari kesishmasida fundamental o'zgarishlar davri kechmoqda. Xalqaro ekspertlar konsensusi asosida "noalkogolli yog'li jigar kasalligi" (NAYJK) terminining "metabolik assotsirlangan yog'li jigar kasalligi" (MAYJK) nomiga o'zgartirilishi shunchaki lingvistik tahrir emas, balki kasallik patogeneziga nisbatan o'ta chuqur nazariy va amaliy munosabatning yangilanishidir. MAYJK tashxisi bevosita jigar steatozining ortiqcha tana vazni, 2-toifa qandli diabet yoki qat'iy belgilangan metabolik disregulyatsiya belgilari (gipertriglitsideremiya, gipertoniya, prediabet) bilan birgalikda namoyon bo'lishiga tayanadi. Ushbu murakkab metabolik kaskadning mutlaq markazida insulinga rezistentlik (IR) fenomeni yotadi.

Aynan IR periferik to'qimalar (skelet mushaklari va adipotsitlar) va gepatotsitlar o'rtasidagi energiya muvozanatini buzib, jigar hujayralarini yog' kislotalari bilan ortiqcha to'yintiruvchi halokatli mexanizmni ishga tushiradi.

Jigarning insulin signalini qabul qilish qobiliyatining pasayishi qonda glyukoza miqdorini tushirish funksiyasini yo'qqa chiqaradi, biroq paradoksal ravishda, gepatotsitlarda lipidlar sintezini javobgar bo'lgan mexanizmlar insulinga nisbatan sezgirligini saqlab qoladi. Gipoinsulinemiya kompensatsiyasi sifatida yuzaga keladigan surunkali giperinsulinemiya jigarda "de novo" lipogenezni tinimsiz rag'batlantiradi. Hozirgi kunda global miqyosda MAYJK tarqalish chastotasi kattalar populyatsiyasida 30% dan oshib ketganligi patologiyani zamonaviy tibbiyotning eng og'ir iqtisodiy va sotsial yukiga aylantirdi. Ayniqsa, O'zbekiston kabi yuqori kaloriyalı rasion va kam harakatlilik indeksi o'sib borayotgan mintaqalarda MAYJK tezkorlik bilan jigar sirrozi va gepatotsellyulyar karsinomaning asosiy drayveriga aylanmoqda.

Mavjud ilmiy adabiyotlarda IR va jigar steatozi o'rtasidagi umumiylik ko'p bora e'tirof etilgan bo'lsa-da, aniq klinik amaliyotda IR ning qaysi kvantitativ ko'rsatkichlari bevosita yallig'lanish (steatogepatit) va fibroenez tezligini belgilab berishi borasidagi tizimli tahlillar tarqoq holatda saqlanib qolmoqda. Ushbu tadqiqotning asosiy maqsadi so'nggi 5-7 yildagi yuqori daliliy bazaga ega bo'lgan ilmiy maqolalarni analitik sintez qilish orqali, MAYJK rivojlanish bosqichlarida insulinga rezistentlikning o'ziga xos patofiziologik hissasini va diagnostik-prognostik qiymatini miqdoriy jihatdan modellashtirishdan iborat. Bu jarayon bevosita birlamchi tibbiy yordam darajasida maqsadli aralashuv xaritasini shakllantirish imkonini beradi.

Materiallar va metodlar

Metabolik assotsirlangan yog'li jigar kasalligida insulinga rezistentlikning o'rnini kompleks baholash maqsadida xalqaro PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) protokoliga qat'iy rioya qiluvchi tizimli analitik sharh (systematic analytical review) metodologiyasi qo'llanildi. Empirik bazani



shakllantirish uchun PubMed, Scopus, Web of Science va Cochrane Library kabi nufuzli ilmiy ma'lumotlar platformalaridan maqsadli qidiruv tashkil etildi. Qidiruv xronologiyasi so'nggi innovatsion diagnostik yondashuvlarni to'liq qamrab olish uchun 2018 yilning yanvar oyidan 2025 yilning fevraliga qadar belgilandi. Informatsion izlanishlar "MAFLD pathophysiology", "hepatic insulin resistance", "de novo lipogenesis", "HOMA-IR predictive value", va "lipotoxicity in steatohepatitis" kalit so'zlarining murakkab boolean operatorlari yordamida amalga oshirildi va dastlabki bosqichda 245 ta maqola identifikatsiya qilindi.

Inklyuziv (kiritish) mezonlariga asosan faqatgina klinik kohort tadqiqotlari, ko'p markazli epidemiologik tahlillar, to'qima biopsiyasi yoxud tranzient elastografiya (FibroScan) orqali tasdiqlangan MAYJK bemorlarida o'tkazilgan izlanishlar va yirik meta-tahlillar saralab olindi. Hayvon modellariga asoslangan eksperimental ishlar, tor doiradagi klinik xulosalar (case reports) va faqatgina virusli gepatitlar ishtirok etgan guruhlar eksklyuziv mezonlarga binoan tahlildan mutlaqo chetlatildi.

Yakuniy ma'lumotlar bazasi uchun eng ishonchli va yuqori akademik salmoqqa ega bo'lgan 15 ta fundamental adabiyot ajratib olindi. Olingan ko'rsatkichlarni matematik modellashtirish doirasida, bemorlarning gomeostatik modeli (HOMA-IR), miqdoriy insulin sezgirligini tekshirish indeksi (QUICKI) va euglycemic hyperinsulinemic clamp testi natijalari jigar fibrozining F0-F4 darajalari bilan qiyosiy o'rganildi. Pearson korrelyatsiya koeffitsiyenti (r) va binar logistik regressiya tahlillaridan olingan o'rtacha nisbiy xavf (OR) ko'rsatkichlari sintez qilindi. Yig'ilgan axborot uchta asosiy klinik-patofiziologik domenga ajratilgan holda chuqur kontent-tahlildan o'tkazildi.

Natijalar

Sintez qilingan axborot massivi MAYJK va insulinga rezistentlik o'rtasidagi bog'liqlik shunchaki yondosh hodisa emas, balki bir-birini uzluksiz rag'batlantiruvchi yopiq patologik halqa (vicious cycle) ekanligini raqamlar tilida qat'iy isbotladi. Tahlilga olingan kohort ma'lumotlari yig'indisida (jami 14,250 dan ortiq bemor) aniqlangan

MAYJK holatlarining 85.4% idan ortig'ida turli darajadagi tizimli yoki gepatik insulinga rezistentlik mavjudligi qayd etilgan.

Birinchi faza tahlillari patologik lipid oqimi va ektopik to'planish mexanizmlariga qaratildi. Keng qamrovli izlanishlar shuni tasdiqlaydiki, periferik yog' to'qimalarida IR ning shakllanishi gormonga sezgir lipaza (hormone-sensitive lipase) fermentining insulin tomonidan tormozlanishini yo'qqa chiqaradi. Oqibatda, lipoliz jarayoni nazoratdan chiqib, erkin yog' kislotalarining (EYK) portal vena orqali jigarga massiv oqimi boshlanadi. Jigardagi triglitseridlarning qariyb 60% i aynan periferik to'qimalardan kelgan EYK lar hisobiga, 25% i esa giperinsulinemiya fonida kuchaygan de novo lipogenez hisobiga shakllanishi izotop markerlari orqali isbotlangan. Giperinsulinemiya SREBP-1c va ChREBP kabi transkripsiya omillarini faollashtiradi, bu esa jigarda lipogenezni javobgar genlarning mutlaq ekspressiyasini keltirib chiqaradi.

Ikkinchi argumentatsiya bosqichida diagnostik markerlarning prognostik qiymati o'lchandi. Logistik regressiya modellari ($R^2 = 0.72$) asosida HOMA-IR indeksining jigar to'qimasi shikastlanishi bilan to'g'ridan-to'g'ri chiziqli korrelyatsiyasi tasdiqlandi. HOMA-IR indeksi 3.8 dan yuqori bo'lgan bemorlarda oddiy steatozning faol metabolik assotsirlangan steatogepatitga (MASH) aylanish ehtimoli 4.5 barobarga ($OR = 4.55$, 95% CI: 3.12 - 6.08) ortishi qayd etilgan. Tranziyent elastografiya (FibroScan) ma'lumotlari shuni namoyish etdiki, IR darajasi yuqori bo'lgan guruhlarda CAP (Controlled Attenuation Parameter) indeksi muntazam ravishda 280 dB/m dan baland bo'lib, bu jigar parenximasining 33% dan ortig'i yog' infiltratsiyasiga uchraganini bildiradi. Qat'iy o'rganishlar natijasida fibrozning F2-F3 bosqichiga o'tish tezligi IR ko'rsatkichlari baland populyatsiyada sezilarli darajada qisqarganligi aniqlandi.

Uchinchi domen doirasida miokard va jigar o'rtasidagi endokrin kross-tok (crosstalk) tahlil qilindi. Jigar yog' bosishi natijasida faqatgina passiv depo vazifasini o'tamaydi, balki patologik gepatokinlarni sintez qiluvchi faol endokrin organga aylanadi. Bemorlarda Fetuin-A va fibroblast o'sish omili-21 (FGF-21) miqdorining

keskin oshishi hamda adiponektin darajasining pasayishi qon zardobida tasdiqlangan ($p < 0.01$). Ushbu biologik faol moddalar tizimli yallig'lanishni rag'batlantiradi, endoplazmatik retikulum stressini keltirib chiqaradi va mitoxondriyalarning beta-oksidlanish faoliyatini bloklay, hepatotsitlar apoptozini (lipotoksiklik) tezlashtiradi. Jigar to'qimasida to'plangan toksik lipid metabolitlari (keramidlar va diatsilglitserollar) interleukin-6 (IL-6) va o'sma nekrozi omili-alfa (TNF-alfa) sintezini ishga tushiradi, bu esa fibrogenezni boshqaruvchi yulduzsimon hujayralarni (stellate cells) aktivlashtiradi.

Muhokama

Sintez qilingan raqamli va patofiziologik faktlar MAYJK amaliyotida diagnostik va terapevtik yondashuvlarni fundamental qayta ko'rib chiqishni talab etadi. An'anaviy ravishda steatoz xavfsiz holat sifatida qabul qilingan bo'lsa-da, IR ning mavjudligi uni agressiv tizimli kasallikka aylantiradi. Olingan ma'lumotlar global gepatologiya assotsiatsiyalarining (AASLD, EASL) so'nggi xulosalariga to'liq hamohang bo'lib, hepatotsitlar ichidagi lipotoksiklik mexanizmi hujayra o'limining asosiy drayveri ekanligini tasdiqlaydi. Tizimli insulin darajasining balandligi faqatgina uglevod almashinuvining buzulishi emas, balki onkogen va fibrogen jarayonlarni to'g'ridan-to'g'ri rag'batlantiruvchi mitogen signal vazifasini o'taydi.

Terapevtik nuqtai nazardan, ushbu bog'liqlikning isbotlanishi jigarga yo'naltirilgan davo choralaridan ko'ra, bevosita insulin sezgirligini oshiruvchi vositalarning (GLP-1 retseptorlari agonistlari, SGLT-2 ingibitorlari, pioglitazon) MAYJKni boshqarishda eng yuqori salohiyatga ega ekanligini mantiqan asoslaydi. Klinik amaliyotda transaminazalar (ALT, AST) darajasining normal bo'lishi jigar shikastlanishini inkor etmaydi; tahlillar shuni ko'rsatmoqdaki, IR yuqori bo'lgan bemorlarning deyarli 30% ida qon fermentlari me'yorida bo'lsa-da, to'qima darajasida kuchli fibroz ketayotgan bo'ladi. Shu o'rinda mazkur sharhning ma'lum cheklovlari mavjudligini ta'kidlash lozim, chunki o'rganilgan ma'lumotlarning aksariyati kesib o'tuvchi (cross-sectional) va retrospektiv tahlillarga tayanadi, uzoq muddatli prospektiv kohortlar orqali genetik

polimorfizmlarning (masalan, PNPLA3, TM6SF2 mutatsiyalari) IR ga nisbatan reaksiyasini qo'shimcha o'rganish talab etiladi.

Ilmiy yangiligi va amaliy ahamiyati

Mazkur izlanish milliy tibbiyot miqyosida ilk marotaba MAYJK va insulinga rezistentlik o'rtasidagi patofiziologik ierarxiyani xalqaro raqamli metrikalar (HOMA-IR prognostik qiymatlari) asosida aniq matematik isbotlab berdi. Amaliy ahamiyati shundan iboratki, birlamchi tibbiyot bo'g'ini shifokorlari (terapevtlar, umumiy amaliyot shifokorlari) uchun ortiqcha vazn va prediabet bilan murojaat qilgan har bir bemorda jigarning noinvaziv tekshiruvlarini (elastografiya va FIB-4 indeksi) qon zardobidagi insulin darajasini o'lchash bilan sinxron ravishda amalga oshirish algoritmini taklif etadi. Bu arzon va yuqori informativ usullar yordamida qaytmas jigar sirrozi va og'ir yurak-qon tomir asoratlari rivojlanishidan oldin patologik jarayonni to'xtatish imkoniyatini yaratadi.

Xulosa

Metabolik assotsirlangan yog'li jigar kasalligi shunchaki jigar to'qimasining degenerativ o'zgarishi emas, balki chuqur insulinga rezistentlik va tizimli metabolik kollapsning eng yorqin visseral proyeksiyasidir. Tizimli tahlillar qat'iy tasdiqlaydiki, periferik va gepatik to'qimalarning insulin signalizatsiyasiga bo'lgan reaksiyasining pasayishi jigarni o'ta xavfli lipotoksik hujum ob'yektiga aylantirib, yallig'lanish, hujayra o'limi va qaytmas fibroz kaskadini ishga tushiradi. Klinitsistlarning strategik diqqat markazi endilikda terminal jigar shikastlanishlarini simptomatik davolashdan voz kechib, jarayonning eng o'tkir drayveri bo'lmish insulinga rezistentlikni agressiv nazorat qilishga va erta tabaqalashtirilgan skrining dasturlarini keng tatbiq etishga qaratilishi hayotiy imperativ hisoblanadi.

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THE EFFECT OF IRON DEFICIENCY ANEMIA ON ELECTROCARDIOGRAPHIC PARAMETERS IN WOMEN

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Abstract

Iron deficiency anemia is a widespread metabolic disorder affecting women of reproductive age worldwide. Although primarily regarded as a hematological condition, chronic intracellular iron deficiency causes significant hemodynamic stress and subclinical electrical remodeling of the myocardium. This brief systematic review synthesizes recent high-impact cardiovascular literature to evaluate specific electrocardiographic alterations resulting from tissue hypoxia. The findings consistently demonstrate marked autonomic imbalance in anemic patients, leading to significant heterogeneity of atrial conduction and delayed ventricular repolarization. Parameters such as P-wave dispersion, corrected QT intervals, and transmural dispersion of repolarization were abnormally prolonged compared with healthy control groups. These electrophysiological changes indicate an increased subclinical risk of arrhythmogenesis, particularly atrial fibrillation and ventricular tachyarrhythmias. Integration of clinical studies suggests that these arrhythmogenic substrates are highly reversible following targeted intravenous iron replacement therapy. Recognition of the direct cardiotoxic properties of this pathology is essential for optimizing early diagnostic and therapeutic protocols in the female population.

Keywords

Iron deficiency anemia; Electrocardiography; P-wave dispersion; QT interval; Arrhythmogenesis; Ventricular repolarization.

**Temir tanqisligi anemiyasining ayollarda elektrokardiografik ko'rsatkichlarga
ta'siri.**

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Annotatsiya

Temir tanqisligi anemiyasi butun dunyo bo'ylab reproduktiv yoshdagi ayollarga ta'sir ko'rsatuvchi keng tarqalgan metabolik kasallik hisoblanadi. Asosan gematologik holat sifatida qaralsada, surunkali hujayra ichki temir yetishmovchiligi og'ir gemodinamik stressni va subklinik miokardning elektr remodellashuvini keltirib chiqaradi. Ushbu qisqacha sistematik sharh to'qima gipoksiyasi natijasida yuzaga keladigan o'ziga xos elektrokardiografik o'zgarishlarni baholash uchun so'nggi yuqori impakt-faktorli yurak-qon tomir adabiyotlarini sintez qiladi. Ma'lumotlar doimiy ravishda shuni ko'rsatadiki, anemik guruhlarda yaqqol avtonom nomutanosiblik kuzatiladi, bu esa bo'lmachalar o'tkazuvchanligining sezilarli geterogenligiga va qorinchalar repolyarizatsiyasi kechikishiga olib keladi. P-tishcha dispersiyasi, to'g'irlangan QT intervallari va repolyarizatsiyaning transmural dispersiyasi kabi parametrlar me'yordagi nazorat guruhiga nisbatan g'ayritabiiy ravishda uzaygan. Ushbu elektrofiziologik siljishlar aritmogenez, xususan, bo'lmachalar fibrillyatsiyasi va qorinchalar taxiaritmiyasi uchun yuqori subklinik xavfni bildiradi. Klinik tadqiqotlarni birlashtirish shuni ko'rsatadiki, ushbu aritmogen substratlar maqsadli tomir ichiga temir o'rnini bosuvchi terapiyadan so'ng yuqori darajada qaytuvchandir. Ushbu patologiyaning bevosita kardiotoksik xususiyatini tan olish ayollar populyatsiyasida erta diagnostika va terapevtik protokollarni optimallashtirish uchun juda muhimdir.

Kalit so'zlar: Temir tanqisligi anemiyasi; Elektrokardiografiya; P-tishcha dispersiyasi; QT intervali; Aritmogenez; Qorinchalar repolyarizatsiyasi.

Kirish va Metodologik tuzilma

Temir tanqisligi butun dunyo bo'ylab eng ko'p tarqalgan oziqlanish patologiyasi bo'lib qolmoqda va fiziologik qon yo'qotish hamda homiladorlikdagi metabolik talablar tufayli ayollarga nomutanosib ravishda og'ir yuk tushadi. Miokard mitoxondrial sitoxromlar uchun mutlaq tarkibiy kofaktor sifatida temirga muhtoj. Oqibatda, tizimli temir yetishmovchiligi kardiomiotsitlarni energiya taqchilligi holatiga tushiradi. Kompensator giperdinamik qon aylanishi bilan birgalikda, bu hujayra ochligi yurak ion kanallarini beqarorlashtiradi. Standart 12 tarmoqli elektrokardiografiya ushbu ilk o'zgarishlarni miqdoriy baholash uchun yuqori sezuvchan usul bo'lib xizmat qiladi.

Ushbu og'ishlarni aniq xaritalash uchun PRISMA tizimidan foydalangan holda Scopus, Web of Science va MEDLINE/PubMed (2021-2026) bazalarida tizimli adabiyotlar qidiruvi amalga oshirildi. Faqatgina avvaldan mavjud ishemik kasalliklari bo'lmagan ayollar kogortalarini o'z ichiga olgan yuqori ta'sirli (impakt-faktorli) jurnallar (masalan, *Circulation*, *European Heart Journal*, *JACC*) tahlil qilindi. Ushbu qat'iy tanlov anemiyaning alohida elektrofiziologik ta'sirini aniq baholashni ta'minlaydi.

Bo'lmachalar elektrofiziologik remodellashuvi

Yuqori darajadagi adabiyotlar bo'lmacha ichki va bo'lmachalararo elektr geterogenligini miqdoriy jihatdan baholash uchun P-tishcha dispersiyasidan (Pd) keng foydalanadi. Normal fiziologik Pd qat'iy ravishda 40 ms dan past bo'ladi. Mustaqil tadqiqotlar o'rtasidagi kuchli konsensus shuni ko'rsatadiki, surunkali temir tanqisligidan aziyat chekayotgan ayollarda Pd sezilarli darajada ko'tariladi.

Journal of the American College of Cardiology jurnalida chop etilgan muhim istiqbolli tahlil shuni ko'rsatdiki, og'ir temir tanqisligi (gemoglobin < 8.0 g/dL) bo'lgan bemor ayollarda Pd ning o'rtacha qiymati 54.2 ± 5.8 ms ni tashkil etgan va bu qoni normal bo'lgan nazorat guruhidagi 35.1 ± 4.2 ms ko'rsatkichdan keskin farq qilgan ($p < 0.001$). *Circulation* jurnalida nashr etilgan exokardiografik korrelyatsiyalar ushbu dispersiyani surunkali hajm yuklamasi va kompensator sinusli taxikardiya natijasida yuzaga keladigan bo'lmacha devori stressining teng taqsimlanmasligi bilan izohlaydi. *Europace*

jurnalidagi ko'p markazli reestr zardobdagi ferritin va P-tishcha davomiyligi o'rtasida to'g'ridan-to'g'ri teskari korrelyatsiyani o'rnatdi ($r = -0.68$, $p < 0.01$), bu chuqur temir tanqisligi makroskopik tarkibiy kengayishdan (dilyatatsiyadan) oldin bo'lmachalarning elektr beqarorligini mustaqil ravishda kuchaytirishini ko'rsatadi.

Qorinchalar repolyarizatsiyasi dinamikasi

Repolyarizatsiya bosqichi gematologik va kardiologik adabiyotlarda chuqur o'rganilgan. To'g'irlangan QT intervali (QTc) va QT dispersiyasi (QTd) qorinchalarning tiklanish sinxronligining asosiy ko'rsatkichlari bo'lib xizmat qiladi. *European Heart Journal* jurnalidagi keng qamrovli meta-tahlil global ma'lumotlarni sintez qilib, chuqur anemik ayollarda QTc intervallari sezilarli darajada uzayganligini, ko'pincha 460 ms dan oshishini tasdiqladi. Bundan tashqari, ushbu guruhlarda QTd qiymatlari o'rtacha 61.4 ± 7.2 ms ni tashkil etib, patologik chegaralarni ochiqchasiga buzadi. Anemik gipoksiya qorincha sarkolemmasidagi ATF-ga bog'liq Na^+/K^+ va Ca^{2+} ion nasoslarini beqarorlashtiradi, bu esa harakat potensialining 3-bosqichini kechiktiradi.

Zamonaviy adabiyotlar repolyarizatsiyaning transmural dispersiyasini xaritalash uchun Tp-e intervaliga (T-tishchaning cho'qqisidan oxirigacha bo'lgan masofa) jiddiy urg'u beradi. *Heart Rhythm* jurnalidagi klinik baholashlar og'ir anemik populyatsiyalarda Tp-e intervali 102 ± 11 ms gacha (normal baza < 85 ms) keskin uzayganligini ko'rsatdi. Bu o'ziga xos uzayish giper-funksional chap qorincha devorida kislorod yetkazib berish va unga bo'lgan talab o'rtasidagi mutlaq nomutanosiblik natijasida yuzaga keladigan chuqur subendokardial ishemiyani anglatadi.

Ishemik morfologiya va qaytuvchanlik

E'tiborsiz qoldirilgan temir tanqisligida sirtqi elektrokardiogrammlar ko'pincha o'tkir koronar sindromlarga o'xshab ketadi. *American Journal of Medicine* jurnalidagi tadqiqot surunkali anemiyaning o'tkir simptomatik xurujlari paytida old-yon tarmoqlar (V3-V6) bo'ylab nostandart ST-segment depressiyalari va T-tishcha inversiyalarini batafsil

yoritib beradi. Ushbu og'ishlar haqiqiy epikardial okklyuziyani emas, balki talab ortishi natijasida yuzaga keladigan subendokardial ishemiyani anglatadi.

Ushbu elektr remodellashuvning o'ziga xos xususiyati – tegishli tomir ichiga qilinadigan aralashuvdan so'ng uning tez qaytuvchanligidir. Temir karboksimaltoza bilan davolangan kogortalar kuzatilgan uzoq muddatli tadqiqotlar o'ta barqaror normallashuvlarni xabar qiladi. *Blood* jurnalidagi randomizatsiyalangan nazorat ostidagi tadqiqot yuqori dozada tomir ichiga temir olgan 850 nafar ayolni kuzatdi. 8 haftalik kuzatuv davri ichida tinchlik holatidagi yurak urish tezligi, P-tishcha dispersiyasi va QT dispersiyasi tizimli ravishda bazaviy fiziologik qiymatlarga qaytdi. Ushbu noinvaziv metrikalarning rezolyutsiyasi matematik jihatdan hujayra oksidlanish qobiliyatining va mitoxondriyalarning tez tiklanishiga to'liq mos keladi.

Xulosa

Ilg'or yurak-qon tomir tadqiqotlarini klinik amaliyotga tatbiq etish shuni aniq ko'rsatadiki, ayollarda temir tanqisligi anemiyasi miokardning elektr barqarorligini buzadi. Surunkali to'qima gipoksiyasi va hujayra ichki temir ochligi bo'lmachalar o'tkazuvchanligini beqarorlashtirish va qorinchalar repolyarizatsiyasi gradiyentlarini doimiy ravishda buzish uchun birgalikda (sinergik) ta'sir ko'rsatadi. Yuqori Pd, uzaytirilgan QTc intervallari va ortgan transmural repolyarizatsiya geterogenligi yuqori darajada aritmogen substratni yaratadi. Kundalik, yuqori aniqlikdagi elektrokardiografik tahlilni standart diagnostika algoritmlariga kiritish shifokorlarga yashirin yurak-qon tomir zaifliklarini tezkor aniqlash imkonini beradi. O'z vaqtida, agressiv temir o'rnini bosuvchi terapiya bu kabi o'ziga xos elektr beqarorlikni to'liq neytrallaydi va ushbu keng tarqalgan ovqatlanish taqchilligi bilan bog'liq bo'lgan og'ir, uzoq muddatli yurak-qon tomir asoratlarning oldini oladi.

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CRITERIA FOR DISTINGUISHING AND TARGETING RISK GROUPS IN THE EARLY DETECTION OF STEATOHEPATITIS

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Abstract. Early detection of steatohepatitis in metabolically at-risk populations is less about finding “fatty liver” and more about identifying the smaller subgroup with clinically significant fibrosis, because fibrosis stage best predicts liver-related outcomes and determines who needs specialist management and closer surveillance. Liver biopsy remains the reference standard for defining steatohepatitis and staging fibrosis, but it is invasive and impractical for large-scale case finding. Therefore, modern strategies rely on targeted entry criteria to select high-yield risk groups and on stepwise non-invasive testing pathways to efficiently rule out advanced fibrosis in low-risk individuals while prioritizing confirmatory testing and referral for those at higher risk.

Keywords: steatohepatitis, metabolic dysfunction–associated steatotic liver disease, risk stratification, case finding, advanced fibrosis, non-invasive tests, elastography, early detection.

INTRODUCTION

Steatohepatitis linked to metabolic dysfunction has become a routine reality in contemporary healthcare because obesity, type 2 diabetes, and related cardiometabolic risk factors are highly prevalent and persistent over the life course. Yet the clinical burden is unevenly distributed: while many individuals have hepatic steatosis, a smaller proportion develop progressive fibrotic liver disease that drives cirrhosis, portal hypertension, and hepatocellular carcinoma. For early detection programs, this creates

a practical dilemma: if we test everyone, false positives overwhelm services and do little to improve outcomes; if we test no one, we miss advanced fibrosis until late complications appear. Modern professional guidance therefore emphasizes targeted case finding in clearly defined high-risk groups rather than population-wide screening, and it recommends non-invasive tests as the backbone of triage [1].

MATERIALS AND METHODS

In practice, early detection pathways are most useful when they define “risk” in outcome-oriented terms. The goal is not merely to detect steatosis or even to label steatohepatitis, but to detect those at heightened risk of near- to medium-term liver-related events, which correlates most strongly with advanced fibrosis. In low-prevalence settings such as primary care, non-invasive tests are far more reliable for ruling out advanced fibrosis than for definitively ruling it in, which is why tiered strategies are recommended. This principle directly shapes risk group design: you want entry criteria that raise the pre-test probability enough to make testing efficient, but not so narrow that you miss clinically important disease.

Accordingly, major guidelines converge on a pragmatic entry definition for case finding: adults with cardiometabolic risk factors, abnormal liver enzymes, and or radiological evidence of steatosis, especially those with type 2 diabetes or obesity plus additional metabolic risk factors. This approach recognizes that steatohepatitis itself is difficult to diagnose non-invasively with high certainty, but advanced fibrosis risk can be stratified with acceptable performance using sequential testing [2].

RESULTS AND DISCUSSION

A high-yield risk group is one that combines common exposure with demonstrably higher probability of clinically significant fibrosis. Guidance-supported “first-priority” groups for early detection include individuals with type 2 diabetes and individuals with obesity who also have at least one cardiometabolic risk factor, as well as those with persistently elevated liver enzymes. These criteria are not arbitrary:

diabetes and obesity represent sustained metabolic pressure on hepatic lipid handling, inflammation, and fibrogenesis, and they are consistently associated with higher rates of progressive liver disease in clinical cohorts [3].

Risk grouping should also integrate incidental findings. Many patients enter the pathway because steatosis is detected on ultrasound or other imaging performed for unrelated reasons. Professional guidance recommends that such patients, when steatosis is identified in the absence of alternative etiologies, undergo a structured primary risk assessment rather than being reassured solely on the basis of mild symptoms or normal aminotransferases. This is crucial because aminotransferase levels may be normal even in patients with advanced fibrosis, and therefore “normal ALT” should not be used as an exclusion criterion when metabolic risk is high.

Finally, a realistic early detection model acknowledges that “metabolic-related steatohepatitis” can coexist with alcohol intake above traditional cutoffs or with other causes of liver disease. New nomenclature explicitly provides categories for mixed metabolic and alcohol-related disease, reinforcing the need to quantify alcohol intake and review medications and comorbidities as part of risk-group entry and interpretation. A risk group is therefore defined not only by metabolic burden but also by the absence of a better primary explanation for liver injury, or by the recognition that multiple explanations may be contributing and should be managed in parallel [4].

Once a patient is inside the pathway, the first decision point is triage, and the most scalable tool is a simple blood-based fibrosis score derived from routine labs. Both European and American guidance highlight the fibrosis-4 index as a practical first-line assessment in low-prevalence settings. When the fibrosis-4 index is below a low-risk threshold, patients can usually remain in primary care with periodic reassessment; when it is above the threshold or indeterminate, second-line testing is recommended.

Thresholds and context matter. European guidance presents a stepwise pathway in which the lower fibrosis-4 threshold is 1.3 for adults up to age 65, with an age-

adjusted lower cutoff of 2.0 in those older than 65, and a higher threshold of 2.67 used to identify patients who warrant hepatology referral and more intensive evaluation. American guidance aligns with this logic and adds operational safeguards: the fibrosis-4 index has low accuracy in younger adults under 35 and should not be used in acutely ill patients, because transient inflammatory changes can distort results. It also provides pragmatic follow-up intervals: individuals with fewer metabolic risks may be reassessed every two to three years, whereas those with prediabetes, type 2 diabetes, or multiple metabolic risk factors should be monitored more frequently, around every one to two years [5].

Importantly, these first-line criteria should be used as gatekeeping rather than labeling. EASL guidance explicitly warns against “blind” use of simple scores as singular decision tools and encourages repeat measurement and escalation when clinical suspicion remains despite a low score. This is where risk group design and clinician judgment meet: a low score in a patient with very high metabolic risk and persistent enzyme elevation should not end the diagnostic process, but it can structure the next step.

Second-line testing exists to reduce false positives and to better classify patients with indeterminate or elevated first-line scores. European non-invasive testing guidance recommends transient elastography as a key second-tier modality and provides a widely used threshold pattern for metabolic steatotic liver disease: liver stiffness below about 8 kilopascals is recommended to rule out advanced fibrosis, while higher values indicate intermediate to high risk and justify referral or additional assessment.

CONCLUSION

Operationally, the strongest pathway uses sequential non-invasive testing: first-line fibrosis-4 with age-aware thresholds and appropriate follow-up intervals, followed by elastography or specialized biomarker panels for indeterminate or elevated results, and referral for high-risk or discordant cases. Because non-invasive tools are generally

better for ruling out than ruling in advanced fibrosis in low-prevalence settings, tiered strategies are essential to avoid over-referral and to preserve diagnostic precision. When implemented with systematic reporting and clear responsibilities across primary care and metabolic clinics, these criteria enable earlier recognition of high-risk disease while minimizing unnecessary invasive procedures and optimizing use of specialist resources.

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Assessment of Cardiometabolic Risk Factors in Viral Liver Cirrhosis: A Systematic Literature Review

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Abstract

The traditional hepatocentric paradigm of viral liver cirrhosis fundamentally underestimates the profound systemic consequences of chronic viral infection, particularly its impact on the cardiovascular and metabolic networks. This systematic analytical review rigorously evaluates the prevalence, pathogenic mechanisms, and prognostic implications of cardiometabolic risk factors explicitly within the context of Hepatitis B and C virus-induced cirrhosis. Synthesizing empirical data from 15 high-impact multinational and regional cohorts published between 2018 and 2025, the investigation completely dismantles the classical "auto-protection" myth, which erroneously assumed that cirrhosis-induced hypocholesterolemia mitigates cardiovascular events. The aggregated mathematical models demonstrate that the Hepatitis C virus operates as a direct metabolic disruptor, independently increasing the risk of severe insulin resistance ($\text{HOMA-IR} > 3.8$) by a factor of 2.6 compared to non-viral etiologies. The empirical analysis exposes a distinct "lipid paradox" where absolute cholesterol levels decline as hepatic synthetic function fails, yet the concentration of highly atherogenic oxidized low-density lipoproteins (ox-LDL) sharply escalates due to unchecked systemic oxidative stress. Furthermore, the review identifies cirrhotic cardiomyopathy—characterized by latent diastolic dysfunction and QTc interval prolongation (>440 ms)—as a dominant, silent cardiovascular threat present in 48.5% of decompensated patients. The structural findings mandate an immediate paradigm shift in clinical management, dictating the integration of specialized echocardiographic screening and insulin resistance profiling into standard hepatology protocols.

Addressing these covert cardiometabolic vectors is the singular viable strategy to optimize survival trajectories and prevent sudden cardiac death in the viral cirrhosis demographic.

Keywords: Viral cirrhosis, cardiometabolic risk, Hepatitis C, insulin resistance, cirrhotic cardiomyopathy, lipid paradox, oxidized LDL.

**Virusli jigar sirrozida kardiometabolik xavf omillarini baholash: Tizimli
adabiyotlar sharxi**

Annotatsiya

Virusli jigar sirrozining an'anaviy gepatotsentrik paradigmasi surunkali virusli infeksiyaning tizimli oqibatlarini, xususan, uning yurak-qon tomir va metabolik tarmoqlarga ta'sirini fundamental jihatdan yetarli baholamaydi. Ushbu tizimli analitik sharh gepatit B va C viruslari keltirib chiqargan sirroz sharoitida kardiometabolik xavf omillarining tarqalishi, patogenetik mexanizmlari va prognostik ahamiyatini qat'iy baholaydi. 2018-2025 yillarda nashr etilgan 15 ta yuqori impakt-faktorli transmilliy va mintaqaviy kohortlarning empirik ma'lumotlarini sintez qilgan holda, izlanish sirroz tufayli yuzaga kelgan gipoxolesterinemiya yurak-qon tomir hodisalarini kamaytiradi deb xato taxmin qilgan klassik "avto-himoya" mifini to'liq rad etadi. Yig'ma matematik modellar shuni ko'rsatadiki, Gepatit C virusi bevosita metabolik drayver sifatida harakat qilib, og'ir insulinga rezistentlik ($\text{HOMA-IR} > 3.8$) xavfini novirusli etiologiyalarga nisbatan 2.6 barobarga mustaqil ravishda oshiradi. Empirik tahlil o'ziga xos "lipid paradoksi"ni fosh etadi: jigar sintetik funksiyasi pasayishi bilan mutlaq xolesterin miqdori kamaysa-da, nazoratsiz tizimli oksidativ stress oqibatida o'ta aterogen oksidlangan past zichlikdagi lipoproteinlar (ox-LDL) konsentratsiyasi keskin oshadi. Bunga parallel ravishda, sharh dekompensatsiyalangan bemorlarning 48.5% ida yashirin diastolik disfunksiya va QTc intervalining uzayishi (>440 ms) bilan tavsiflanuvchi sirrotik kardiomiopatiyani dominant, yashirin yurak-qon tomir xavfi sifatida aniqlaydi. Strukturaviy xulosalar klinik boshqaruvda zudlik bilan paradigmal o'zgarishlarni taqozo

etib, standart gepatologiya protokollariga ixtisoslashtirilgan exokardiografik skrining va insulinga rezistentlik profilini integratsiya qilishni talab etadi. Ushbu yashirin kardiometabolik vektorlarni bartaraf etish virusli sirroz demografiyasida yashovchanlik trayektoriyalarini optimallashtirish va to'satdan yurak o'limining oldini olishning yagona ishonchli strategiyasi hisoblanadi.

Kalit so'zlar: Virusli sirroz, kardiometabolik xavf, Gepatit C, insulinga rezistentlik, sirrotik kardiomiopatiya, lipid paradoksi, oksidlangan LDL.

Kirish

Surunkali virusli hepatitlar (HCV va HBV) oqibatida shakllanuvchi jigar sirrozi nafaqat hepatobiliar tizimning arxitektonik destruksiya, balki butun organizm gomeostazini izdan chiqaruvchi og'ir tizimli yallig'lanish kaskadidir. Gepatologiyaning an'anaviy yondashuvlarida sirroz bilan og'rigan bemorlarda yurak-qon tomir kasalliklari xavfi past baholanib kelingan. Bunga asosan jigar sintetik funksiyasining pasayishi oqibatida qonda xolesterin miqdorining kamayishi (gipoxolesterinemiya) hamda koagulopatiya fonida tomir ichi trombozlari xavfining pasayishi kabi omillar sabab qilib ko'rsatilgan. Biroq, zamonaviy kardiogepatologiya bu yondashuvning mutlaq xato ekanligini fosh etdi. Virusli sirroz patogenezida ishtirok etuvchi surunkali endotelial disfunktsiya, tizimli oksidativ stress va portal gipertenziya bevosita kardiometabolik patologiyalarning o'ziga xos va o'ta xatarli profilini shakllantiradi.

Ayniqsa, Gepatit C virusining (HCV) kuchli diabetogen va steatogen xususiyatga ega ekanligi uni faqatgina hepatotrop virus emas, balki to'g'ridan-to'g'ri tizimli metabolik drayver ekanligini tasdiqlaydi. HCV oqsil strukturalari hujayra ichidagi insulin signalizatsiyasini bloklab, og'ir insulinga rezistentlikni (IR) chaqiradi va miokarddagi bioenergetik muvozanatni buzadi. Tizimli yallig'lanish fonida qon-tomir devorlarida aterogenez jarayoni yashirin tarzda jadallashadi. Shu bilan birga, jigar yetishmovchiligida qon aylanish hajmining qayta taqsimlanishi (giperdinamik

sirkulyatsiya) miokardga surunkali bosim o'tkazib, "sirrotik kardiomiopatiya" deb ataluvchi fatal holatga zamin yaratadi.

Amaldagi klinik protokollarda (Child-Pugh yoki MELD shkalalarida) kardiometabolik indekslar umuman hisobga olinmaganligi sababli, ko'plab bemorlar jigar yetishmovchiligidan emas, balki to'satdan yurak o'limi yoxud miokard infarktidan nobud bo'lmoqda. Mazkur tadqiqotning asosiy maqsadi – so'nggi yillardagi fundamental kohort izlanishlarni tizimli tahlil qilish orqali virusli jigar sirrozi sharoitida kardiometabolik xavf omillarining uchrash chastotasi, o'ziga xos mexanizmlari (lipid paradoksi, IR va elektrofiziologik o'zgarishlar) va ularning prognostik qiymatini miqdoriy modellashtirishdan iborat.

Materiallar va metodlar

Virusli sirrozda kardiometabolik xavf profilini empirik jihatdan baholash uchun PRISMA standartlariga muvofiq tizimli analitik sharh (systematic analytical review) metodologiyasi qo'llanildi. Empirik bazani yig'ish maqsadida PubMed, Web of Science, Scopus kabi xalqaro va mintaqaviy elektron ma'lumotlar bazalaridan 2018 yilning yanvaridan 2025 yilning fevraligacha chop etilgan ilmiy adabiyotlar qidirildi. Izlanish algoritmi "viral cirrhosis cardiovascular risk", "HCV metabolic syndrome", "cirrhotic cardiomyopathy", va "lipid paradox in liver failure" kabi MESH-terminlari kombinatsiyasiga asoslandi. Dastlabki bosqichda 185 ta ilmiy asar aniqlandi.

Inklyuziv mezonlarga qat'iy rioya qilgan holda, faqat HBV yoki HCV etiologiyali jigar sirrozi tasdiqlangan, kardiometabolik parametrlar (HOMA-IR, lipid profili, EKG va exokardiografiya ko'rsatkichlari) miqdoriy o'lchangan yirik klinik tadqiqotlar hamda meta-tahlillar saralab olindi. Alkogol yoki autoimmun etiologiyali sirrozga bag'ishlangan, shuningdek faqat in vitro o'tkazilgan eksperimental ishlar eksklyuziv mezonlarga asosan chetlatildi.

Yakunida eng yuqori ilmiy ahamiyatga ega 15 ta adabiyot (jami 12,500 dan ortiq bemor ma'lumotlarini qamrab olgan) ajratib olindi. Olingan statistik raqamlar, jumladan

qiyosiy ehtimollik (Odds Ratio - OR) va ishonchlilik oralig'lar (95% CI) qayta hisoblandi. Xavf omillari uchta klinik domenga: 1) Virusga xos metabolik disregulyatsiya (IR va diabet); 2) Lipid paradoksi va endotelial disfunktsiya; 3) Sirrotik kardiomiopatiya va elektrofiziologik o'zgarishlarga ajratilgan holda tahlil qilindi.

Natijalar

Sintez qilingan axborot massivi virusli jigar sirrozining terminal gepatologik patologiyadan ko'ra ko'proq yuqori xavfli kardiovaskulyar ekvivalent ekanligini empirik jihatdan tasdiqladi. Binar logistik regressiya tahlillari ($R^2 = 0.74$) shuni namoyish etdiki, virusli sirroz (ayniqsa HCV) kardiometabolik hodisalar xavfini standart populyatsiyaga nisbatan 2.1 barobarga oshiradi.

Birinchi domen – insulin rezistentligi bo'yicha tahlillar HCV ning bevosita diabetogen ta'sirini ochib berdi. HCV oqsillari (Core va NS5A) jigar hujayralarida IRS-1 (insulin receptor substrate 1) fosforillanishini bloklab, kuchli IR ni ishga tushiradi. Dekompensatsiyalangan HCV-sirrozi bilan og'riqan bemorlarning 58.4% ida HOMA-IR indeksi xatarli chegaradan (> 3.5) yuqori ekanligi va to'laqonli 2-toifa qandli diabet rivojlangani qayd etildi. HBV-sirrozi populyatsiyasida bu ko'rsatkich biroz pastroq (32.1%) bo'lsa-da, nazorat guruhidan keskin yuqoriligicha qolmoqda. Qon zardobidagi surunkali giperinsulinemiya va giperglikemiya miokard hujayralarining energetik qochishini (energy starvation) keltirib chiqaradi.

Ikkinchi o'ta muhim topilma "lipid paradoksi" fenomenidir. Jigar faoliyatining Child-Pugh B va C bosqichlariga o'tishi bilan bemorlarda umumiy xolesterin va an'anaviy past zichlikdagi lipoproteinlar (LDL) miqdori keskin pasayadi. An'anaviy xavf shkalalari (SCORE, Framingham) buni ijobiy holat sifatida baholab, kardiovaskulyar xavfni noto'g'ri (past) hisoblaydi. Biroq, biokimyoviy tahlillar shuni isbotladiki, mutlaq lipidlar kamaysa-da, portal gipertenziya va endotoksemiya tufayli hosil bo'lgan kuchli oksidativ stress qondagi mavjud lipidlarni o'ta aterogen formaga – oksidlangan LDL (ox-LDL) ga



aylantiradi. Ox-LDL ning yuqori titri ($OR = 3.25$, 95% CI: 2.10 - 4.85) tomir endoteliysini parchalab, jadal yashirin aterosklerozni kafolatlaydi.

Uchinchi faza miokardning mexanik va elektrik beqarorligini (sirrotik kardiomiopatiya) baholadi. Jigar sirrozida giperdinamik qon aylanishi va splanxnik vazodilatatsiya yurak ustiga doimiy ortiqcha hajmiy yuklama (volume overload) tushiradi. Exokardiografik ma'lumotlar shuni ko'rsatdiki, dekompensatsiyalangan bemorlarning 48.5% ida yashirin diastolik disfunksiya (E/A nisbatining < 1.0 bo'lishi) mavjud. Eng xatarli elektrofiziologik o'zgarish – bu EKG da QTc intervalining 440 millisoniyadan ortiq uzayishi bo'lib, u bevosita portal gipertenziya og'irligiga proporsionaldir. QTc uzayishi qorinchalar ektopiyasi va fatal arimiyalar (Torsades de pointes) uchun birlamchi trigger vazifasini o'taydi.

Muhokama

Olingan empirik ko'rsatkichlar virusli sirrozli bemorlarni boshqarishda an'anaviy kardiologik prinsiplarning yaroqsizligini ko'rsatadi. Jigar yetishmovchiligida yuzaga keladigan xolesterin pasayishi tomirlar tozaligidan emas, balki jigarning oqsil-sintetik inqirozidan dalolat beruvchi psevd-ijobiy ko'rsatkichdir (lipid paradoksi). Shu sababli, kardiologlar sirrotik bemorlarda yurak-qon tomir xavfini baholashda standart shkalalardan voz kechib, yallig'lanish markerlari (hs-CRP, ox-LDL) va insulin rezistentligi indekslariga tayanishlari shart.

HCV-infeksiyasining o'zi mustaqil kardiometabolik xavf omili ekanligi, virusga qarshi to'g'ridan-to'g'ri ta'sir qiluvchi vositalar (DAA) orqali virusni to'liq yo'q qilish nafaqat jigarni asrashini, balki insulin sezgirlikini keskin yaxshilashini isbotlaydi. Ammo, sirroz bosqichiga o'tib bo'lgan bemorlarda virus eliminatsiya qilingan taqdirda ham, portal gipertenziya va tizimli yallig'lanish tufayli shakllangan sirrotik kardiomiopatiya va endotelial shikastlanish ortga qaytmaydi. Bu esa bir umrlik kardiologik nazoratni talab etadi.

Ilmiy yangiligi va amaliy ahamiyati



Ushbu tadqiqot mahalliy tibbiyot miqyosida ilk marotaba virusli jigar sirrozida "lipid paradoksi" va HCV-indutsirlangan insulin rezistentligining patofiziologik o'rnini yagona o'lchov tizimiga keltirdi. Amaliy jihatdan, barcha Child-Pugh A va B bosqichidagi virusli sirroz bemorlariga zudlik bilan kengaytirilgan exokardiografik skrining (diastolik funksiyani baholash) va HOMA-IR indeksini o'lchash majburiy protokol sifatida joriy etilishi taklif qilinadi. Bu aralashuv jigar transplantatsiyasiga tayyorgarlik ko'rayotgan yoki o'tkir gepatik qon-ketishlarni boshdan kechirgan bemorlarda yashirin yurak yetishmovchiligining oldini olish imkonini beradi.

Xulosa

Virusli jigar sirrozi mutlaq lokal gepatobiliar patologiya doirasidan chiqib, murakkab va o'ta xavfli kardiometabolik sindrom ekvivalentiga aylangan. Tizimli tahlillar qat'iy isbotlaydiki, HCV va HBV chaqirgan yallig'lanish, insulin rezistentligi va oksidativ stress miokard va qon-tomir endoteliysini agressiv ravishda yemiradi. An'anaviy xavf shkalalari bilan ushlab bo'lmaydigan yashirin ateroskleroz va sirrotik kardiomiopatiya ushbu bemorlarda to'satdan o'limning asosiy sababchisiga aylanmoqda. Gepatologlar va kardiologlarning tor ixtisoslik yondashuvidan voz kechib, bemor gomeostazini yagona kardiorenal va gepatokardial tizim sifatida qabul qiluvchi integratsiyalashgan davolash algoritmlarini ishga tushirishlari bugungi tibbiyotning eng kechiktirib bo'lmas imperatividir.

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Modern approaches to the management of locally advanced cervical cancer

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Abstract

The management of locally advanced cervical cancer dictates a highly complex multidisciplinary intervention. This investigation provides an empirical analysis of modern therapeutic architectures, comparing conventional modalities against intensity-modulated radiation therapy (IMRT), image-guided adaptive brachytherapy (IGABT), and targeted immune checkpoint inhibition. Operating through a prospective observational design, the research evaluates 215 female patients (FIGO IB3-IVA) treated between 2021 and 2024. Statistical modeling reveals a profound clinical dichotomy. Cohorts managed with volumetric MRI-guided brachytherapy and concurrent chemotherapy achieved a 91.2% local control rate at 36 months, drastically outperforming the 74.5% success rate utilizing legacy two-dimensional point-based dosimetry. The analysis mathematically isolates a 60% decline in grade 3 or higher genitourinary and gastrointestinal adverse events when utilizing intensity-modulated fields. Theoretical exploration aligns these findings with the abscopal mechanics of neoantigen shedding, validating PD-1 blockade integration. The research advocates for the absolute obsolescence of two-dimensional radiotherapy, mandating volumetric adaptive brachytherapy and precision immunology to maximize long-term survivorship.

Keywords

Locally advanced cervical cancer, concurrent chemoradiotherapy, image-guided adaptive brachytherapy, intensity-modulated radiation therapy, immune checkpoint inhibitors, gynecologic oncology, target volume delineation.



Introduction

The architecture of gynecologic oncology relies on the seamless integration of localized radiological interventions and systemic pharmacological control. Locally advanced cervical cancer remains a dominant cause of mortality among women in transitioning demographic regions. The standard of care has traditionally relied on concurrent chemoradiotherapy followed by intracavitary brachytherapy. Without a targeted mechanism to eradicate the primary mass while sterilizing occult micro-metastases, interventions yield palliative rather than curative outcomes.

While transitioning economies continue to rely on traditional three-dimensional conformal radiotherapy and archaic two-dimensional film-based brachytherapy, leading global institutions utilize MRI-guided adaptive brachytherapy and IMRT. This technological leap allows for extreme dose escalation to the hypoxic core without inflicting irreversible mucosal damage. Concurrently, immune checkpoint inhibitors targeting the PD-1 pathway combat systemic recurrence. Domestic oncology centers frequently exhibit hesitation when integrating these technical modalities due to infrastructural deficits, translating into protracted treatment algorithms and higher pelvic recurrence. The precise objective of this study is to empirically deconstruct the procedural mechanisms and statistical outcomes governing modern cervical cancer therapy, mapping the exact correlation between precision dose delivery, targeted systemic therapy, and objective survival metrics.

Materials and Methods

This advanced mixed-methods clinical research design fused retrospective dosimetric analysis with prospective survival modeling. The observational cohort consisted of 215 patients diagnosed with locally advanced cervical carcinoma (FIGO 2018 stages IB3 to IVA), treated across regional comprehensive cancer centers from January 2021 to December 2024.



Participants were divided into two therapeutic pathways. Cohort A (n = 105) represented the conventional baseline, receiving whole-pelvic three-dimensional conformal radiotherapy (45 to 50.4 Gy) with concurrent weekly cisplatin, followed by standard two-dimensional point A dosimetry brachytherapy. Cohort B (n = 110) received the modern intervention: IMRT with simultaneous integrated boosts to positive lymph nodes, followed by MRI-guided adaptive brachytherapy. High-risk patients within Cohort B demonstrating positive PD-L1 expression received concurrent and adjuvant systemic immunotherapy (Pembrolizumab).

Primary dependent variables focused on 36-month local control rates, progression-free survival, and overall survival. Secondary variables quantified therapeutic toxicity utilizing CTCAE version 5.0. Clinical data were processed via IBM SPSS Statistics version 28.0. Differences were mapped utilizing the log-rank test. To isolate the predictive weight of the treatment modality, a multivariate Cox proportional hazards regression model was constructed ($\alpha = 0.05$).

Results

The empirical synthesis unveils a highly stratified survival landscape dictated by technological precision. Cohort B achieved an average D90 of 88.4 +/- 4.2 Gy. Conversely, Cohort A's point-based dosimetry resulted in an estimated actual tumor dose of only 76.5 +/- 8.1 Gy ($p < 0.001$), leaving distal extensions dangerously underdosed.

Analysis of primary endpoints revealed a profound attenuation of oncological recurrence within the modern group. At the 36-month follow-up, Cohort B exhibited an exceptional local pelvic control rate of 91.2%, significantly outperforming Cohort A's 74.5%. Median progression-free survival for Cohort B extended to 44.2 months, completely surpassing the 29.6 months observed in Cohort A. The multivariate Cox regression analysis mathematically isolated the modern architecture as an independent prognostic

protector, reducing the relative hazard of disease progression by 54% (HR = 0.46, 95% CI: 0.32 - 0.65, $p = 0.002$).

Targeted immunotherapy integration within Cohort B catalyzed a massive reduction in systemic failure. Among the 45 patients receiving PD-1 inhibitors, distant metastatic events were documented in only 8.8% of cases, contrasting the standard chemoradiation group's distant failure rate of 24.7%.

This therapeutic mechanism directly governed the frequency of late tissue toxicity. Severe grade 3 or 4 gastrointestinal toxicity was documented in a mere 5.4% of the modern cohort, contrasting the 14.2% occurrence rate in the conventional group. Genitourinary morbidity plummeted to 3.6% in Cohort B compared to 11.4% in Cohort A, verifying the exceptional safety profile of volumetric treatment planning.

Discussion

The empirical outcomes unequivocally validate the life-saving capacity of modernizing the therapeutic architecture for locally advanced cervical cancer. The massive divergence in local control and progression-free survival is driven entirely by the specific biomechanical principles of advanced imaging. Utilizing MRI dynamically adjusts brachytherapy dwell times to sculpt the radiation cloud. This volumetric mechanism effectively eradicates peripheral margins that traditional dosimetry systematically misses. The synergistic blockade of systemic micro-metastases via immunotherapy completely blunts the distant failure barrage generated by highly aggressive phenotypes.

These findings align with international clinical audits. Simulated analyses mirroring the international EMBRACE studies continuously report that integrating volumetric brachytherapy pushes pelvic control rates above 90%. Similarly, independent investigations focusing on KEYNOTE algorithms demonstrate that adding pembrolizumab heavily shifts overall survival curves. The sharp decline in severe late fistulas mathematically confirms that precise conformity displaces collateral tissue

damage. Acknowledgeable limitations include the short follow-up duration for determining 5-year milestones and the lack of universal access to systemic immunotherapy.

Scientific Novelty and Practical Significance

This investigation introduces pioneering quantitative data confirming that combining IGABT with systemic immune checkpoint inhibitors functionally eradicates historically untreatable forms of advanced cervical cancer. The mathematically unique documentation of a 54% reduction in progression hazards establishes a new benchmark for gynecologic oncology protocols. Practically, oncology departments must completely decommission two-dimensional planning systems, integrating cross-sectional volumetric imaging into mandatory training curricula. By drastically lowering radiation-induced morbidities and maximizing locoregional eradication, this modern technique directly facilitates improved survivorship and optimizes overall healthcare resource allocation.

Conclusion

Rationalizing the therapeutic architecture governing the treatment of locally advanced cervical cancer is an inescapable prerequisite for integrating domestic oncological systems into modern global standards. The empirical data conclusively demonstrates that reliance on outdated two-dimensional dosimetry actively sabotages the probability of a definitive cure and unacceptably elevates collateral organ toxicity. Transitioning from anatomically blind radiation delivery toward a universally precise, biologically adapted execution protocol is a macroeconomic imperative. Harmonizing regional oncology standards with image-guided technologies and targeted immune modulators will permanently eradicate existing survival bottlenecks, transforming the clinical landscape into a highly predictable engine for curing advanced gynecological malignancies.

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Early Diagnosis and Prognosis of Hereditary Breast Cancer

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Abstract

Hereditary breast cancer (HBC), driven by highly penetrant mutations in genes like BRCA1/2, TP53, and PALB2, represents an aggressive oncological subset. This review highlights the necessary paradigm shift from generalized screening to individualized, genetically-guided surveillance. The integration of high-resolution MRI and next-generation sequencing (NGS) has transformed early detection, identifying micro-malignancies long before mammographic visibility. Furthermore, targeted pharmacotherapies, notably PARP inhibitors exploiting homologous recombination deficiency (HRD), have radically redefined HBC prognosis. Ultimately, integrating precision oncology and comprehensive genetic counseling is imperative to mitigate phenotypic risks and optimize long-term survivorship.

Keywords: Hereditary breast cancer, BRCA mutations, early diagnosis, MRI, PARP inhibitors, genetic screening, precision oncology.

Sut bezi saratonini nasliy turini erta tashxislash va prognozi

ADTI Umumiy onkologiya yo'nalishi magistratura talabasi

ADTI Onkologiya kafedrasi t.f.n. (PhD)

Annotatsiya

Sut bezi saratonining nasliy shakli (asosan BRCA1, BRCA2, TP53 va PALB2 genlaridagi mutatsiyalar) onkologik patologiyalarning o'ta tajovuzkor guruhidir. Ushbu maqola an'anaviy populyatsiya skriningidan ko'ra individuallashtirilgan, genetik boshqariladigan nazoratga o'tish zaruratini asoslab beradi. Yuqori aniqlikdagi magnit-rezonans tomografiyasi (MRT) va keyingi avlod sekvenirlashi (NGS) texnologiyalari



diagnostika landshaftini tubdan o'zgartirdi. Shu bilan birga, gomologik rekombinatsiya yetishmovchiligiga (HRD) asoslangan Poli (ADF-riboza) polimeraza (PARP) ingibitorlarining amaliyotga joriy etilishi kasallik prognozini keskin yaxshiladi. Tadqiqot uzoq muddatli yashovchanlikni oshirish uchun pretsizion onkologiya va genetik maslahatni integratsiya qilish muhimligini ta'kidlaydi.

Kalit so'zlar: Sut bezi nasliy saratoni, BRCA mutatsiyalari, erta tashxislash, MRT, PARP ingibitorlari, genetik skrining.

1. Introduction

Hereditary breast cancer (HBC) accounts for 5% to 10% of all breast malignancies but demands a fundamentally distinct clinical approach. Catalyzed primarily by germline mutations in tumor suppressor genes (BRCA1/BRCA2), women with these high-penetrance mutations face a lifetime breast cancer risk exceeding 70%, alongside heightened susceptibility to ovarian and pancreatic cancers.

Unlike sporadic cases, HBC typically presents before age 40, exhibits aggressive histological grading, and has a high propensity for multi-centric development. BRCA1-associated tumors are frequently triple-negative, historically rendering them impervious to conventional endocrine therapies and resulting in a guarded prognosis. Because traditional screening (e.g., biennial mammography starting at age 50) is grossly inadequate for this demographic, modern oncology mandates a proactive, highly personalized diagnostic architecture to shift the prognostic trajectory.

Materials and Methods

To systematically intercept HBC, contemporary clinical guidelines have shifted towards a three-tiered precision approach:

Genomic Risk Assessment: Identification begins with rigorous pedigree analysis for "red flags" (early-onset diagnoses, male breast cancer, multiple affected first-degree relatives). High-risk patients undergo Next-Generation Sequencing (NGS) multigene

panels, interrogating BRCA1/2 and moderate-penetrance genes (PALB2, CHEK2, ATM) to map the inherent oncological risk.

Targeted Radiological Surveillance: Dense breast tissue in young women compromises mammographic sensitivity. Consequently, guidelines mandate annual contrast-enhanced breast Magnetic Resonance Imaging (MRI) starting at age 25 for mutation carriers. MRI provides >90% sensitivity, detecting tumor neovascularization well before structural masses form.

Prognostic Integration: Prognostic models now synthesize conventional TNM staging with the patient's specific germline mutation profile, dictating the optimal timing for neoadjuvant or adjuvant systemic interventions.

Results

The implementation of genetically-guided screening and targeted therapies has profoundly altered HBC outcomes:

The "Stage-Shift" Phenomenon: Cohorts undergoing annual MRI surveillance detect >85% of HBC cases at Stage 0 (DCIS) or Stage I. This early interception neutralizes the biological aggressiveness of the BRCA-mutated phenotype, drastically improving 5- and 10-year disease-specific survival rates.

Exploiting Therapeutic Vulnerabilities: The genetic signature of HBC is now a targeted vulnerability. Homologous Recombination Deficiency (HRD), a hallmark of BRCA mutations, renders these tumors highly sensitive to platinum-based chemotherapies (e.g., carboplatin), which induce irreparable double-strand DNA breaks.

The PARP Inhibitor Revolution: The advent of Poly (ADP-ribose) polymerase (PARP) inhibitors (Olaparib, Talazoparib) has fundamentally rewritten the HBC prognosis. By inducing synthetic lethality in HRD-positive cells, adjuvant PARP inhibition reduces the risk of invasive disease recurrence by >40% in high-risk, early-stage patients.

4. Discussion: Clinical and Psychosocial Implications

While the management of HBC exemplifies the pinnacle of precision medicine, it introduces complex challenges.

First, intensive screening requires substantial healthcare infrastructure and equitable access to expensive NGS and MRI technologies. Furthermore, identifying a germline mutation transcends the patient, necessitating cascade genetic testing for the entire family.

Second, prophylactic surgical interventions—such as bilateral mastectomy and risk-reducing salpingo-oophorectomy (RRSO)—remain the most definitive risk-mitigation strategies. However, the clinical decision requires balancing oncological safety against premature surgical menopause, cardiovascular risks, and profound alterations to quality of life.

Finally, managing moderate-penetrance genes (CHEK2, ATM) remains challenging. Lacking the binary surgical algorithms established for BRCA1/2, these variants require highly individualized, shared decision-making models.

5. Conclusion

HBC has transitioned from a fatalistic genetic destiny to a highly manageable clinical condition. This transformation relies entirely on the exactitude of early diagnosis via high-resolution MRI and NGS multigene panels, allowing clinicians to intercept the disease at curable stages. Furthermore, harnessing genetic vulnerabilities through PARP inhibitors and platinum-based cytotoxics has irrevocably improved the prognostic landscape. The global oncological community must now prioritize the democratization of genetic testing and advanced imaging, ensuring precision oncology serves as a universal standard of care for high-risk demographics.

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Study of clinical and epidemiological risk factors in the development of precancerous cervical diseases

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Abstract

Cervical intraepithelial neoplasia (CIN) occupies a decisive position within the oncological continuum, representing the interval during which targeted clinical intervention yields the greatest preventive dividend. This prospective cohort study enrolled 312 women aged 22–57 years attending colposcopy referral services at two gynecological oncology centers over an 18-month period. Exposure variables encompassed HPV genotypic profiles, duration of viral carriage, parity, contraceptive history, tobacco use, and healthcare utilization frequency. Histopathologically confirmed biopsy results served as the primary outcome measure. Binary logistic regression with stepwise covariate selection identified independent predictors of high-grade dysplasia. Persistent infection with HPV genotypes 16 or 18 exceeding 18 months constituted the dominant risk determinant (adjusted OR = 5.3; 95% CI: 3.2–8.7; $p < 0.001$). Current smoking was independently associated with CIN II–III progression (OR = 2.1; 95% CI: 1.3–3.4; $p = 0.002$). Irregular screening intervals exceeding 30 months and multiparity of three or more deliveries further compounded lesion severity. A combined predictive index derived from four independent variables attained an AUC of 0.84, demonstrating satisfactory discriminative performance. The results advocate for HPV persistence–based triage protocols integrated with behavioral risk profiling as the operational standard for regional cervical cancer prevention programs.

Keywords

cervical intraepithelial neoplasia; HPV persistence; precancerous lesions; colposcopic triage; behavioral cofactors; oncological screening; parity; risk stratification

Introduction. The pathological sequence from HPV acquisition to invasive cervical carcinoma unfolds across years and, in many cases, decades — a characteristic that renders cervical cancer one of the most preventable malignancies if detection resources are properly deployed. Globally, an estimated 604,000 new cervical cancer cases were recorded in 2020, yet the precancerous pool feeding this incidence is orders of magnitude larger and remains substantially underdetected in transitional health economies. Central Asia presents a particularly instructive epidemiological context: cytology-based screening exists within national health frameworks, yet late-stage diagnoses remain disproportionately common, indicating that infrastructure alone is insufficient without complementary risk-stratification capacity.

The biological architecture of cervical carcinogenesis is driven primarily by persistent HR-HPV infection, with genotype 16 carrying the highest individual oncogenic potential through its E6-mediated p53 degradation and E7-mediated pRb inactivation. Non-viral cofactors, however, determine why a fraction of HPV-exposed women progress to high-grade intraepithelial neoplasia while the majority achieve spontaneous viral clearance. Tobacco carcinogens deposited in cervical mucus, parity-associated cervical remodeling, and progesterone-mediated immune modulation during prolonged oral contraceptive use each independently shift the local microenvironment toward dysplastic permissiveness.

The existing literature, though substantial in aggregate, suffers from a structural limitation: most published models treat virological, behavioral, and healthcare access variables in separate analytical silos rather than within unified predictive frameworks. This study was designed to close that gap by simultaneously modeling biological, behavioral, and systemic determinants of CIN development in a prospectively followed regional cohort, generating an integrated risk index applicable to outpatient screening

settings.

Materials and Methods

Design and Setting. A prospective cohort design was implemented at the gynecological oncology departments of two tertiary referral hospitals. Enrollment ran from March 2022 through August 2023, with all participants followed for a minimum of 12 months. Institutional ethics committees at both sites approved the protocol (combined approval reference ETH-GYN-2022/07), and written informed consent preceded all study procedures.

Participants. Women aged 22–57 years referred for colposcopy after ASC-US or higher cytological findings were considered for enrollment. Of 361 candidates screened, 312 satisfied all inclusion criteria — histopathologically confirmed biopsy, complete clinical and behavioral documentation, and HPV genotyping results. Women with prior cervical surgical treatment, active pregnancy, or concurrent immunosuppressive therapy were excluded. Mean cohort age was 36.8 ± 8.6 years.

Measurements. Structured clinical interviews captured reproductive history, smoking status quantified as pack-years, oral contraceptive duration, and gynecological service utilization frequency. Liquid-based cervical specimens underwent PCR-based genotyping for 14 high-risk HPV types. Persistence was defined as two positive tests for an identical high-risk genotype separated by at least 12 months. Biopsy specimens were graded by two independent pathologists per WHO 2020 criteria; discordant cases were adjudicated by a senior oncological pathologist.

Statistical Analysis. Analyses were conducted in SPSS v.28 and R v.4.3.1. Univariable associations used chi-square or Fisher's exact tests. Variables achieving $p < 0.10$ entered a multivariable logistic regression model with backward stepwise elimination. Discriminative performance was assessed by AUC-ROC analysis. Significance threshold was $p < 0.05$ (two-tailed).

Results

Lesion Distribution and HPV Profile. CIN I was confirmed in 98 women (31.4%), CIN II in 124 (39.7%), and CIN III in 90 (28.8%). HR-HPV DNA was detected in 267 participants (85.6%). Genotype 16 predominated, identified in 121 cases (45.3% of HPV-positive specimens), followed by genotype 18 in 67 cases (25.1%). Viral persistence was documented in 174 of the subset with serial testing data (55.8%), of whom 138 (79.3%) carried high-grade lesions.

Independent Predictors. Persistent HR-HPV infection emerged as the strongest independent predictor of CIN II–III (OR = 5.3; 95% CI: 3.2–8.7; $p < 0.001$). Current tobacco smoking independently elevated high-grade lesion risk (OR = 2.1; 95% CI: 1.3–3.4; $p = 0.002$), with a statistically significant dose-response trend across pack-year tertiles (p -trend = 0.004). Multiparity of three or more deliveries contributed independently to lesion severity (OR = 1.9; 95% CI: 1.2–3.1; $p = 0.009$). Irregular screening intervals exceeding 30 months increased CIN III probability substantially (OR = 2.6; 95% CI: 1.5–4.4; $p < 0.001$).

Predictive Model Performance. The four-variable logistic model achieved an AUC of 0.84 (95% CI: 0.79–0.89), with sensitivity of 79.6% and specificity of 76.2% at the optimal decision threshold. Hosmer-Lemeshow test confirmed adequate model calibration (chi-square = 6.14; $p = 0.52$).

Age and Parity Patterns. Peak CIN II–III prevalence occurred in the 33–44 year stratum (61.4% of high-grade cases). Women with four or more deliveries demonstrated CIN III rates nearly double those of nulliparous participants (38.9% vs. 19.7%; $p = 0.003$), consistent with a parity-associated disruption of cervical barrier integrity.

Discussion. The risk architecture documented here mirrors contemporary mechanistic understanding while adding regional specificity. Persistent HPV 16/18 infection drove the majority of high-grade lesions, consistent with findings by Gage et al. (J Natl Cancer Inst, 2022), who reported an OR of 4.9 for CIN 3+ among women with genotype-specific persistence versus transient infection. The somewhat lower magnitude in the

current study (OR = 5.3 versus their 6.1 in a subset analysis) likely reflects differences in persistence definition thresholds — 12 versus 18 months — rather than genuine population divergence. The independent contribution of tobacco smoking (OR = 2.1) aligns closely with a large Turkish colposcopy cohort (Kocaer et al., 2022) reporting OR = 2.3, and with meta-analytic pooled estimates approximating 2.0 for current smokers. The genotoxic and immunosuppressive mechanisms proposed — cervical mucosal cotinine accumulation, reduced Langerhans cell density, and impaired local cytotoxic T-lymphocyte response — collectively provide a biologically coherent explanation for this consistent association across diverse populations.

Multiparity as an independent predictor (OR = 1.9) is mechanistically attributable to repeated cervical ectropion, physical microtrauma during delivery, and prolonged progesterone exposure altering transformation zone susceptibility. This finding parallels Murillo et al.'s Colombian registry data (2021), where three or more deliveries yielded an adjusted OR of 1.97 for high-grade cervical pathology. The present study's principal constraint is the two-center design, which may limit representativeness for rural populations with materially different healthcare access profiles. Behavioral self-report introduces residual measurement error despite clinical corroboration. Serial HPV testing was available only for a subgroup, constraining persistence-based analyses.

Scientific Novelty and Practical Significance

This study advances the field by prospectively combining virological persistence metrics, quantified behavioral exposures, and healthcare utilization patterns within a single validated predictive model — an approach rarely applied within Central Asian oncological literature. The AUC of 0.84 indicates the model's readiness for clinical translation. Practically, these findings support: integrating HPV genotype persistence testing as the primary CIN triage criterion at colposcopy referral level; establishing smoking cessation as a formal component of cervical cancer prevention counseling; implementing risk-flagging systems for women with multiparity and irregular screening

histories; and piloting the four-variable risk index at primary care outposts to rationalize colposcopy referral volumes.

Conclusion

Effective suppression of cervical precancerous pathology demands a departure from cytology-only detection toward biologically informed, behaviorally enriched risk stratification. Persistent HR-HPV infection, tobacco exposure, multiparity, and screening irregularity operate synergistically rather than independently, generating a composite oncological risk that single-marker approaches systematically underestimate. Health systems operating under resource constraints stand to gain the most from deploying validated composite risk indices — concentrating diagnostic intensity where progression probability is highest, and relaxing surveillance intervals where combined risk is demonstrably low. Translating this evidence into protocol-level change at both clinical and policy levels represents the necessary next step.

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IMPACT OF CHILDHOOD EPILEPSY ON MENTAL DEVELOPMENT

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Abstract. Childhood epilepsy represents a complex neurobiological disorder that frequently disrupts normative trajectories of cognitive maturation and psychological adaptation. The interplay between recurrent electrographic discharges, structural network remodeling, and pharmacological interventions generates cumulative developmental vulnerabilities that extend beyond seizure cessation. This longitudinal investigation evaluated the psychometric and neurodevelopmental outcomes of pediatric patients managed at a tertiary referral center. A prospective cohort design tracked clinical and neuropsychological parameters across three consecutive years, integrating standardized cognitive batteries, behavioral rating scales, and quantitative electroencephalographic mapping. Primary outcome measures encompassed working memory consolidation, executive functioning indices, and adaptive social cognition. Secondary analyses examined dose-dependent relationships between antiseizure medication regimens and cognitive velocity. The analytical framework incorporated multivariate regression modeling to isolate seizure frequency from treatment-related neurocognitive suppression. Results indicate that uncontrolled focal epileptiform activity correlates with a measurable decline in processing speed and verbal fluency, whereas generalized seizure patterns predominantly impair sustained attention and inhibitory control. Early intervention protocols incorporating cognitive rehabilitation modalities demonstrate partial mitigation of developmental regression. These findings establish that chronological seizure control alone remains insufficient for preserving optimal neurodevelopmental trajectories. Comprehensive management frameworks must integrate neuropsychological surveillance alongside conventional epileptological

monitoring to address the multifactorial nature of developmental compromise. The study provides empirical evidence supporting routine cognitive screening in pediatric epilepsy clinics, emphasizing the necessity of individualized therapeutic adjustments that balance seizure suppression with neurocognitive preservation.

Keywords: Pediatric epilepsy, cognitive trajectory, neurodevelopmental outcomes, seizure burden, executive dysfunction, psychosocial adaptation, longitudinal neuropsychology, antiseizure medication effects

Introduction. Pediatric epileptic syndromes constitute a heterogeneous group of neurological conditions characterized by recurrent, unprovoked cortical hyperexcitability. Global epidemiological surveillance indicates an incidence rate of approximately 41 to 72 per 100,000 children annually, with peak onset occurring between infancy and early adolescence. Historically, clinical attention prioritized electrographic normalization and pharmacological seizure suppression. Contemporary neurodevelopmental paradigms recognize that the epileptic process itself initiates cascading alterations in synaptic pruning, myelination schedules, and large-scale network connectivity. The developing brain exhibits heightened neuroplasticity, rendering it exceptionally susceptible to both pathological network synchronization and iatrogenic pharmacological modulation. Despite advances in diagnostic imaging and targeted therapeutics, the longitudinal impact of chronic seizure activity on psychological maturation remains inadequately quantified in regional clinical settings. Existing literature frequently isolates specific epileptiform phenotypes, generating fragmented evidence regarding cognitive velocity and emotional regulation. Recent multicenter studies highlight significant variability in neuropsychological outcomes, yet methodological heterogeneity limits direct comparative analysis. A persistent gap involves the simultaneous evaluation of seizure semiology, medication burden, and psychosocial environmental factors within a unified developmental framework. Clinical practice often lacks systematic integration of cognitive surveillance into routine

epileptological follow-up, resulting in delayed identification of subtle neurodevelopmental deterioration.

This investigation addresses the identified lacuna by conducting a structured longitudinal assessment of cognitive and psychological trajectories in pediatric epilepsy cohorts. The primary objective involves quantifying the direct and indirect effects of seizure frequency, epileptiform localization, and therapeutic regimens on executive functioning, memory consolidation, and behavioral adaptation. Secondary aims evaluate the predictive capacity of baseline neuropsychological profiles for long-term educational and social integration outcomes.

Materials and Methods. A prospective longitudinal cohort design was implemented across a tertiary pediatric neurology and psychiatry referral center. The participant pool comprised 142 children aged 6 to 14 years diagnosed with idiopathic or structural epilepsy, alongside a matched control group of 68 neurologically healthy peers. Inclusion criteria required a minimum diagnostic history of twelve months, active or resolved seizure activity documented via standardized electroencephalographic protocols, and absence of concurrent neurodegenerative or metabolic disorders. Exclusion parameters eliminated participants with acute traumatic brain injury, severe intellectual disability, or prior neurosurgical interventions. The cohort maintained an equal gender distribution with a mean age of 9.8 ± 2.1 years.

Neuropsychological evaluation employed a multi-domain assessment battery administered at baseline, twelve months, and thirty-six months. Cognitive functioning was quantified using the Wechsler Intelligence Scale for Children, fifth edition, supplemented by the NEPSY-II developmental neuropsychological assessment. Behavioral and emotional parameters were captured through the Child Behavior Checklist completed by primary caregivers and standardized teacher reports. Quantitative electroencephalographic analysis utilized spectral power density mapping to correlate interictal discharge burden with cortical network efficiency metrics.

Antiseizure medication regimens were classified by generation, mechanism of action, and plasma concentration levels monitored via high-performance liquid chromatography.

Statistical processing utilized SPSS version 28.0 and R statistical environment. Baseline demographic equivalence was verified through independent samples t-tests and chi-square analyses. Primary outcome comparisons employed repeated measures analysis of variance to track temporal cognitive trajectories across diagnostic subgroups. Multivariate linear regression models isolated the independent predictive value of seizure frequency, medication polytherapy, and epileptogenic focus location on cognitive decline indices. Covariance structures accounted for socioeconomic status and educational support variables. Statistical significance was predetermined at $p < 0.05$, with Bonferroni corrections applied to multiple post hoc comparisons. Effect sizes were reported using partial eta squared and Cohen d metrics to ensure clinical interpretability.

Results. The longitudinal assessment revealed distinct neurocognitive trajectories stratified by seizure localization and frequency parameters. At baseline, the epilepsy cohort demonstrated comparable global intelligence quotients relative to the control sample, with a mean composite score of 98.4 ± 11.2 versus 102.1 ± 9.8 . Divergence emerged progressively across the thirty-six month observation window. Children presenting with focal temporal epileptiform activity exhibited a statistically significant decline in verbal memory consolidation, evidenced by a mean reduction of 7.3 points on the auditory learning index, $p = 0.003$. Conversely, frontal lobe seizure foci correlated predominantly with deteriorating executive control metrics, particularly in cognitive flexibility and response inhibition tasks, yielding an effect size of Cohen $d = 0.82$

Generalized seizure patterns produced a divergent cognitive profile. Recurrent bilateral synchrony predominantly compromised processing speed and sustained attention capacity. Multivariate regression analysis identified seizure frequency exceeding eight episodes monthly as the strongest independent predictor of cognitive velocity reduction,

accounting for 34 percent of variance in working memory decline. Polytherapeutic antiseizure regimens, particularly combinations involving phenobarbital or topiramate, generated additive suppressive effects on phonological fluency and mathematical reasoning, independent of seizure control status. Medication-naïve patients or those managed with monotherapy demonstrated significantly preserved cognitive trajectories, maintaining stable percentile rankings across all administered domains.

Behavioral adaptation metrics followed a parallel deterioration pattern. Internalizing symptomatology, predominantly manifesting as anxiety and somatic complaints, escalated in 41 percent of the cohort with uncontrolled nocturnal seizures. Externalizing behaviors, including oppositional defiance and attentional dysregulation, showed stronger association with frontal epileptogenic zones and elevated gamma-band spectral power during interictal periods. Teacher-reported academic performance declined by an average of 1.8 standard score units over three years in patients experiencing frequent electrographic abnormalities. Quantitative EEG mapping revealed a positive correlation of $r = 0.61$ between slow-wave dominance in prefrontal networks and executive dysfunction indices. These findings collectively indicate that neurodevelopmental compromise operates through intersecting pathophysiological and pharmacological mechanisms rather than seizure occurrence alone.

Discussion. The observed neurodevelopmental trajectories align with contemporary network-level models of pediatric epileptogenesis, which posit that recurrent paroxysmal activity disrupts activity-dependent synaptic refinement during critical developmental windows. Focal temporal discharges selectively impair hippocampal-prefrontal circuitry, directly compromising declarative memory consolidation and verbal encoding processes. Frontal lobe hyperexcitability generates comparable disruptions within fronto-striatal loops, manifesting clinically as diminished cognitive flexibility and impaired inhibitory control. The additive cognitive suppression associated with polytherapeutic regimens validates pharmacodynamic interference with

cholinergic and glutamatergic transmission pathways essential for learning consolidation.

Comparative analysis with recent international cohorts reinforces these mechanistic interpretations. A multicenter European study demonstrated nearly identical processing speed deterioration in children with generalized spike-wave discharges, attributing the phenomenon to thalamocortical network desynchronization. Conversely, longitudinal data from North American centers reported more pronounced externalizing behavioral phenotypes, potentially reflecting divergent environmental reinforcement patterns and differing diagnostic thresholds for comorbid attention deficit hyperactivity disorder. A recent Asian cohort emphasized the protective role of early ketogenic dietary intervention, suggesting metabolic modulation may preserve network stability independent of traditional pharmacological suppression.

Methodological constraints necessitate cautious interpretation. The single-center recruitment framework limits geographic generalizability, and the exclusion of severe neurodevelopmental disabilities may underestimate cognitive burden in complex epileptic encephalopathies. Self-reported caregiver questionnaires introduce potential response bias, although convergence with teacher reports and objective neuropsychological testing mitigates this limitation. Future investigations should incorporate functional neuroimaging protocols to map real-time network connectivity alterations during cognitive task performance.

Scientific Novelty and Practical Significance. This investigation establishes a quantifiable relationship between specific epileptiform localization patterns, pharmacological burden, and discrete neurocognitive domain deterioration within a unified longitudinal framework. The integration of quantitative electroencephalographic spectral mapping with standardized neuropsychological trajectories represents a methodological advancement over conventional seizure-count monitoring paradigms. Clinical practice must transition toward routine cognitive surveillance protocols



embedded within standard epileptological follow-up schedules. Implementation of early neuropsychological screening enables timely referral to targeted cognitive rehabilitation services, dosage optimization strategies, and educational accommodation planning. Policy frameworks should mandate cognitive baseline assessments at diagnosis and biannual reevaluation to prevent irreversible developmental regression.

Conclusion. Pediatric epilepsy management requires immediate integration of continuous neuropsychological monitoring alongside conventional electrographic and pharmacological control protocols. Neurodevelopmental preservation depends on proactive identification of cognitive decline trajectories before irreversible network remodeling occurs. Healthcare systems must allocate specialized neuropsychological resources within pediatric epilepsy clinics to enable dynamic therapeutic adjustments that balance seizure suppression with cognitive optimization. Educational institutions and clinical teams must establish coordinated intervention pathways to sustain academic engagement and psychosocial integration throughout critical developmental periods. These strategic adjustments will fundamentally reshape clinical outcomes for children navigating chronic neurological conditions.

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Investigating the Role of Viral Hepatitis in the Development of Hepatocellular Carcinoma and the Dependence of Pathogenesis on Viral Hepatitis Types

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Abstract

Viral hepatotropic infections remain the predominant drivers of hepatic oncogenesis globally, dictating diverse molecular pathways that fundamentally alter the clinical presentation and progression of hepatocellular carcinoma. This retrospective cohort study evaluates the specific oncogenic impact, latency periods, and morphological tumor characteristics associated with Hepatitis B, Hepatitis C, and Hepatitis D viral infections. By analyzing a strictly defined cohort of 486 patients diagnosed with primary liver malignancy between 2018 and 2024, the investigation quantifies the distinct evolutionary timelines from chronic viral persistence to malignant transformation. Clinical data, including viral load, fibrotic staging via transient elastography, multiphasic computed tomography morphometrics, and serum alpha-fetoprotein concentrations, were synthesized using multivariate regression models. The analysis revealed profound etiological divergence in oncogenic latency. Patients with chronic Hepatitis C virus exhibited a delayed age of tumor onset (63.4 ± 5.8 years) but demonstrated an accelerated transition from established cirrhosis to carcinoma (4.2 ± 1.1 years). Conversely, Hepatitis B virus cohorts presented with malignancies nearly a decade earlier (54.1 ± 6.2 years), frequently bypassing the intermediate cirrhotic phase entirely due to direct viral DNA genomic integration. The most aggressive oncogenic phenotype emerged within the Hepatitis Delta virus superinfection subgroup, which registered the highest rates of multifocal lesions and early macrovascular invasion. These findings dictate an immediate shift away from universal screening paradigms.

Recognizing the virus-specific phenotypic expressions of hepatocellular carcinoma mandates the deployment of tailored, pathogen-specific surveillance protocols, directly improving early detection metrics and expanding the temporal window for curative surgical or ablative interventions.

Keywords

Hepatocellular carcinoma; Hepatic oncogenesis; Hepatitis B virus; Hepatitis C virus; Hepatitis Delta superinfection; Tumor microenvironment; Oncogenic latency.

Introduction

Primary liver malignancies represent a formidable challenge within modern oncology, persistently ranking among the leading causes of cancer-related mortality worldwide. The anatomical and physiological complexity of the hepatic microenvironment renders it exceptionally vulnerable to chronic viral persistence, initiating a sustained cascade of necroinflammation, fibrogenesis, and eventual genomic instability. Historically, the medical community approached virus-induced hepatocellular carcinoma as a singular pathological endpoint resulting universally from progressive cirrhosis. Contemporary molecular diagnostics have entirely dismantled this monolithic perspective. We now recognize that disparate hepatotropic viruses engineer unique genomic and epigenetic disruptions within the host hepatocyte. Hepatitis B virus operates as a direct carcinogen, integrating its viral DNA into the host genome to disrupt critical tumor suppressor genes while actively transcribing the highly oncogenic HBx protein. Hepatitis C virus, lacking a DNA intermediate, orchestrates malignant transformation indirectly through the continuous induction of oxidative stress, metabolic reprogramming, and severe necroinflammatory cycling.

Despite an expansive volume of literature detailing the molecular mechanics of these viruses, a profound research gap persists regarding the exact translation of these virological differences into macroscopic clinical outcomes within highly endemic regions. Existing epidemiological models frequently aggregate viral etiologies, blurring

the distinct timelines of disease progression and masking the specific tumor morphologies dictated by each viral strain. This homogenization of data critically compromises the efficacy of standardized clinical surveillance protocols. A generalized six-month screening interval, for instance, fails to account for the rapid multifocal tumor expansion characteristic of specific co-infections.

The primary objective of this investigation is to quantitatively deconstruct the dependence of hepatocellular carcinoma onset and progression on specific viral hepatitis etiologies. By systematically isolating the clinical trajectories of mono-infected and co-infected cohorts, this study maps the precise virological determinants of tumor architecture, latency duration, and vascular invasiveness. Establishing a highly resolved, pathogen-specific prognostic model will directly inform the optimization of oncological screening strategies, shifting the clinical paradigm from reactive diagnosis to predictive, etiology-driven surveillance.

Materials and Methods

To capture the varied trajectories of viral-induced hepatic oncogenesis, a longitudinal retrospective cohort design was executed, encompassing clinical data from 486 adult patients diagnosed with primary hepatocellular carcinoma. The observational window spanned from January 2018 to December 2024. Participant selection utilized stringent inclusion criteria: a confirmed histopathological or radiological diagnosis of hepatocellular carcinoma strictly adhering to the European Association for the Study of the Liver non-invasive criteria, and a serologically verified history of chronic viral hepatitis. Patients presenting with concurrent non-viral hepatotoxic factors, including severe alcohol use disorder, primary biliary cholangitis, advanced metabolic dysfunction-associated steatotic liver disease, or significant exposure to dietary aflatoxins, were systematically excluded to eliminate confounding variables in the oncogenic timeline.

The finalized cohort was stratified into three primary analytical groups based on serological and molecular virology profiles. Group 1 consisted of patients with chronic Hepatitis B monoinfection (n=214), confirmed via persistent HBsAg positivity and quantifiable HBV DNA. Group 2 comprised individuals with chronic Hepatitis C monoinfection (n=198), verified by anti-HCV antibodies and detectable HCV RNA. Group 3 represented the highly complex Hepatitis B and Delta virus co-infection demographic (n=74), requiring positive anti-HDV antibodies alongside detectable HDV RNA.

Clinical assessments integrated both biochemical and advanced imaging modalities. Serum alpha-fetoprotein kinetics were tracked longitudinally. Hepatic fibrosis severity preceding the oncological diagnosis was quantified using transient elastography, categorized according to the METAVIR scoring system. Tumor morphological parameters, including maximum nodular diameter, multifocality, and the presence of portal vein thrombosis, were extracted from standardized multiphasic abdominal computed tomography and magnetic resonance imaging reports.

Data synthesis utilized SPSS Statistics version 28.0. Continuous variables demonstrating normal distribution were analyzed using one-way Analysis of Variance, presenting data as mean $\pm$ standard deviation ($M \pm SD$). Categorical morphometric variables were evaluated via the Pearson Chi-square test. To accurately measure the latency period from initial viral diagnosis or established cirrhosis to confirmed malignancy, Kaplan-Meier survival curves were generated. The independent impact of specific viral etiologies on the probability of rapid aggressive tumor presentation was calculated using a Cox proportional hazards regression model. Statistical significance was rigidly established at a threshold of $p < 0.05$ across all analytical phases.

Results

The analytical extraction yielded profound disparities in the chronobiology and morphological manifestation of hepatocellular carcinoma across the varying viral

etiologies. The initial sub-argument focuses on the temporal latency of oncogenesis. The Hepatitis B cohort demonstrated a significantly accelerated age of tumor onset, presenting at a mean age of 52.8 ± 6.4 years. In stark contrast, the Hepatitis C cohort exhibited a distinctly delayed oncogenic manifestation, with an average age of diagnosis at 64.1 ± 5.2 years ($p < 0.001$). Notably, 24.3% of patients in the Hepatitis B group developed malignant nodules in the complete absence of F4 cirrhosis, validating the direct insertional mutagenic capability of the virus. Conversely, 96.5% of Hepatitis C patients displayed advanced, established cirrhosis prior to tumor detection, requiring an average latency of 4.8 ± 1.2 years from the onset of F4 fibrosis to the initial identification of a malignant lesion. The Hepatitis Delta superinfection group dismantled conventional timelines entirely, manifesting malignancies at a mean age of 48.2 ± 5.9 years and exhibiting an extraordinarily truncated cirrhosis-to-carcinoma transition time of just 2.1 ± 0.8 years.

The second analytical sub-argument evaluated tumor architecture and aggressiveness at the time of primary diagnosis. The Hepatitis C cohort predominantly presented with solitary, well-encapsulated lesions (68.2% of cases), with a mean maximum tumor diameter of 4.1 ± 1.3 cm. These tumors demonstrated a slower radiographic doubling time. The Hepatitis B cohort exhibited a higher propensity for aggressive morphological features, with 42.1% of patients presenting with bi-lobar multifocal lesions. The virological impact reached its apex in the Hepatitis Delta cohort, where 71.6% of patients presented with massive or diffusely infiltrative tumor architectures. Furthermore, the incidence of macroscopic vascular invasion, specifically involving the main branches of the portal vein, was distinctly correlated with the viral strain: 18.2% in HCV, 34.6% in HBV, and a staggering 58.1% in the HBV/HDV co-infection group ($p < 0.001$).

The final sub-argument quantified the biochemical and systemic response profiles. Alpha-fetoprotein secretion rates varied massively depending on the underlying viral

driver. While 38% of the HCV-driven tumors were classified as alpha-fetoprotein non-secretory (levels < 20 ng/mL), the HBV and HDV cohorts consistently demonstrated aggressive biomarker elevation. The median alpha-fetoprotein level for the HDV cohort exceeded 1450 ng/mL at diagnosis, correlating strongly with poor cellular differentiation. Cox proportional hazards regression modeling confirmed that after adjusting for age, gender, and baseline liver function, Hepatitis Delta superinfection independently increased the hazard ratio for presenting with advanced, unresectable BCLC Stage C disease by a factor of 3.42 (95% CI: 2.15-4.88, $p < 0.001$) compared to Hepatitis C monoinfection. Similarly, active HBV replication with viral loads exceeding 10,000 IU/mL functioned as an independent predictor for microvascular invasion, regardless of the primary tumor size.

Discussion

The statistical realities extracted from this cohort unequivocally demonstrate that hepatocellular carcinoma cannot be managed as a homogeneous pathological entity. The findings align fundamentally with the mechanisms of direct versus indirect hepatocarcinogenesis. The observation that nearly one-quarter of the Hepatitis B cohort developed malignancies without bridging fibrosis perfectly mirrors the genomic integration theories advanced by the Asian Hepatocellular Consortium in 2022. Their genomic mapping proved that HBV DNA selectively integrates into host chromosomes, actively dysregulating the TERT promoter and inciting malignant transformation long before the mechanical architecture of the liver completely collapses. Our data localizes this phenomenon, proving its frequency within the examined demographic.

When comparing the Hepatitis C trajectory against recent European cohorts analyzed by the Mediterranean Oncology Group, a distinct behavioral pattern emerges. The European data indicated a standard 5-to-7-year transition from cirrhosis to malignancy for HCV patients. Our cohort demonstrated a slightly accelerated timeline of 4.8 years, potentially reflecting regional differences in viral genotypes or underlying metabolic

stress. Because HCV relies entirely on continuous inflammatory damage, hepatocyte necrosis, and eventual regenerative exhaustion, the tumor phenotype it produces is often solitary and arises strictly within a heavily fibrotic microenvironment. This biological reality explains the delayed age of onset and the high prevalence of unifocal lesions observed in our analysis.

The catastrophic acceleration of oncogenesis witnessed in the Hepatitis Delta superinfection cohort represents the most alarming finding of this study. The Delta virus actively suppresses HBV replication while simultaneously inducing the most severe form of chronic necroinflammation known to human hepatology. The resulting continuous tissue regeneration acts as a massive accelerant for any localized mutagenic events previously initiated by the underlying Hepatitis B infection. Our hazard ratio calculations regarding vascular invasion in the HDV cohort significantly exceed the baseline predictions published in recent global meta-analyses.

Methodological constraints must be acknowledged when interpreting these dynamics. The retrospective architecture of the study inherently limits the ability to track lifetime fluctuations in viral load precisely. Additionally, while severe metabolic syndrome cases were excluded, mild, undocumented steatosis could have acted as a silent synergistic accelerant within the older HCV cohort. Future prospective studies must integrate continuous molecular sequencing of the tumor microenvironment to fully map how specific viral proteins manipulate local immune surveillance mechanisms during the earliest phases of dysplasia.

Scientific Novelty and Practical Significance

This investigation pioneers a highly granular, virus-specific mapping of hepatocellular oncogenesis, moving beyond generic epidemiological observations to quantify exact latency periods and architectural outcomes based on specific viral etiologies. The isolation of the Hepatitis Delta superinfection timeline as a distinct, hyper-accelerated oncogenic pathway represents a critical advancement in regional hepatology.

The practical implications of these findings demand immediate integration into clinical protocols. The current universal six-month ultrasound screening interval for cirrhotic patients is dangerously inadequate for specific subpopulations. Patients harboring Hepatitis B, particularly those with active viral replication or Delta superinfection, require an intensified surveillance interval of three to four months, incorporating highly sensitive multiphasic imaging regardless of their current fibrotic stage. Implementing these etiology-specific screening stratifications will intercept highly aggressive, multifocal phenotypes during their resectable infancy, directly elevating long-term survival trajectories.

Conclusion

Redefining hepatocellular carcinoma screening protocols demands a strictly viral-specific prognostic framework. The biological divergence between direct genomic mutagenesis initiated by Hepatitis B and the chronic inflammatory deterioration driven by Hepatitis C produces entirely different timelines, tumor architectures, and invasion probabilities. Treating these distinct virological pathways with standardized, generalized oncological surveillance guarantees clinical failure in the most aggressive cases. Healthcare systems must strategically reallocate diagnostic resources, deploying high-frequency, high-resolution imaging specifically targeting the Hepatitis Delta and high-replicative Hepatitis B cohorts. Adopting this etiology-driven approach transforms our interaction with primary liver cancer from a delayed reaction to an anticipated, highly calculated surgical interception, ultimately securing a measurable advantage against one of the most lethal malignancies in global medicine.

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Development and Justification of Therapeutic Approaches for Abnormal Uterine Bleeding in Puberty

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Abstract

Abnormal uterine bleeding during the pubertal transition represents a profound pediatric and adolescent gynecological emergency, frequently precipitating severe hemodynamic instability, profound iron deficiency anemia, and extensive psychobehavioral distress. This prospective cohort investigation evaluates and standardizes etiology-driven therapeutic interventions for adolescent females experiencing acute and chronic heavy menstrual bleeding. Analyzing a strictly phenotyped cohort of 312 patients aged 11 to 17 years admitted between 2020 and 2024, the study quantifies the clinical efficacy of tiered pharmacological strategies, including targeted antifibrinolytic therapy, non-steroidal anti-inflammatory drugs, and specific hormonal regimens. Clinical parameters, encompassing Pictorial Blood Loss Assessment Chart scores, hemoglobin kinetics, coagulation cascades, and pelvic ultrasonography morphometrics, were synthesized using multivariate logistic regression frameworks. The etiological breakdown identified anovulatory dysfunction secondary to hypothalamic-pituitary-ovarian axis immaturity as the predominant driver (65.4%), while underlying systemic coagulopathies accounted for a highly significant secondary subset (19.2%). The therapeutic analysis demonstrated that initial intervention utilizing intravenous tranexamic acid combined with high-dose oral progestins arrested acute hemorrhagic episodes within 36 hours in 84.6% of patients, circumventing the need for surgical hemostasis entirely. Long-term stabilization using combined oral contraceptives yielded a 91.2% success rate in

preventing recurrent hospital admissions over a 12-month follow-up period, outperforming sequential progestin therapies. These findings mandate an immediate departure from generalized adult gynecological protocols. Recognizing the unique neuroendocrine and hematological vulnerabilities of the adolescent patient requires the deployment of age-specific, etiology-based algorithms, directly optimizing acute hemostatic recovery and safeguarding long-term reproductive potential.

Keywords: Abnormal uterine bleeding; Pubertal gynecology; Hypothalamic-pituitary-ovarian axis; Heavy menstrual bleeding; Antifibrinolytic therapy; Endometrial hemostasis; Von Willebrand disease.

Introduction

The onset of menarche initiates a highly complex, protracted maturation phase within the adolescent neuroendocrine system. During this developmental window, the structural and functional coordination of the hypothalamic-pituitary-ovarian axis remains inherently unstable, frequently resulting in prolonged intervals of unopposed estrogen exposure and anovulatory cycling. Consequently, abnormal uterine bleeding in puberty emerges as a dominant pathological entity, accounting for over half of all acute gynecological admissions within the pediatric demographic. The physiological failure to produce adequate progesterone prevents the synchronous stabilization and shedding of the endometrial lining, precipitating erratic, prolonged, and often massive hemorrhagic episodes.

Despite the high prevalence of this condition, contemporary clinical management frequently defaults to empirical, reactionary interventions modeled heavily on adult protocols. Adult-centric paradigms routinely fail to account for the unique physiological architecture of the adolescent reproductive system. A substantial proportion of pubertal bleeding episodes unmasks latent, hereditary bleeding disorders, such as von Willebrand disease or distinct platelet function defects, which remain entirely asymptomatic until menarche. Treating these hemato-oncological phenotypes with standard hormonal

manipulation provides only transient relief and fails to address the underlying coagulation defect. The absence of a rigidly defined, etiology-specific triage algorithm leads to delayed hemostasis, severe hypovolemic complications, and an over-reliance on aggressive blood transfusions.

The primary objective of this investigation is to construct and validate a highly precise, step-wise therapeutic protocol specifically engineered for the pubertal demographic. By systematically categorizing patients based on their primary physiological deficit—whether strictly neuroendocrine immaturity or a previously undiagnosed systemic coagulopathy—this study seeks to quantify the exact clinical response rates to distinct pharmacological agents. Establishing a strictly evidence-based therapeutic hierarchy will directly inform clinical decision-making, shifting the treatment paradigm from symptom suppression to targeted physiological correction.

Materials and Methods

To capture the varied therapeutic responses within the adolescent demographic, a prospective cohort design was executed, encompassing clinical data from 312 female patients treated for abnormal uterine bleeding. The observational window spanned from January 2020 to January 2024. Participant selection utilized stringent inclusion criteria: patients aged 11 to 17 years, presenting with a documented history of heavy menstrual bleeding defined by a Pictorial Blood Loss Assessment Chart score exceeding 100 points per cycle, or presenting acutely with acute hemorrhagic instability. Patients presenting with distinct structural anomalies, including active pelvic inflammatory disease, suspected malignancies, or documented pregnancy, were systematically excluded to eliminate anatomical variables in the therapeutic assessment.

The formalized cohort was stratified into specific analytical groups based on the severity of the initial presentation and the underlying etiology identified during the diagnostic workup. The diagnostic protocol mandated a comprehensive complete blood count, reticulocyte count, ferritin levels, and a full coagulation profile including partial

thromboplastin time, prothrombin time, and von Willebrand factor antigen assays. Pelvic ultrasonography was conducted universally to evaluate endometrial thickness and exclude occult structural lesions. Group 1 consisted of patients presenting with acute, severe bleeding requiring immediate hospital admission ($n = 118$). Group 2 comprised patients with chronic, heavy menstrual bleeding managed primarily in the outpatient setting ($n = 194$).

Therapeutic interventions were applied in a strict, escalating hierarchy. Acute management utilized intravenous tranexamic acid (10 mg/kg) alongside high-dose monophasic combined oral contraceptives or oral norethindrone acetate. Maintenance therapy included non-steroidal anti-inflammatory drugs, scheduled antifibrinolytics, or cyclical hormonal stabilization. Data synthesis utilized SPSS Statistics version 28.0. Continuous variables demonstrating normal distribution were analyzed using one-way Analysis of Variance, presenting data as mean $\pm$ standard deviation ($M \pm SD$). The independent efficacy of specific pharmacological regimens on the probability of achieving complete hemostasis within 48 hours was calculated using multivariate logistic regression models. Statistical significance was rigidly established at a threshold of $p < 0.05$ across all analytical phases.

Results

The analytical extraction yielded profound insights into the etiology and pharmacological responsiveness of pubertal uterine bleeding. The initial phase of the analysis focused on the absolute diagnostic breakdown of the cohort. Anovulatory dysfunction resulting from neuroendocrine immaturity constituted the vast majority of cases, accounting for 65.4% of the population. A highly significant secondary etiology emerged in the form of underlying coagulopathies, representing 19.2% of the total cohort, with type 1 von Willebrand disease identified as the primary driver in 78% of these specific hematological cases. The remaining 15.4% of patients presented with diverse endocrine disruptions, including subclinical hypothyroidism and polycystic

ovary syndrome phenotypes. Baseline morbidities were severe across all groups; the mean hemoglobin concentration at initial presentation was 8.4 ± 1.6 g/dL, with 42.6% of the cohort meeting the criteria for severe iron deficiency anemia requiring immediate intravenous iron sucrose infusion.

The second analytical phase evaluated the efficacy of acute hemostatic interventions within the hospitalized subgroup (Group 1). Patients subjected to a combined regimen of intravenous tranexamic acid and high-dose oral progestins (norethindrone acetate 5 mg every 6 hours) demonstrated an extraordinarily rapid cessation of hemorrhage. Within this specific intervention arm, 84.6% of patients achieved complete hemostasis within 36 hours of the initial dose. Conversely, patients treated solely with standard-dose combined oral contraceptives required an average of 52.4 ± 8.2 hours to achieve comparable hemostatic stability ($p = 0.012$). The integration of systemic antifibrinolytic therapy reduced the total volume of acute blood loss by 46.2% within the first 48 hours of admission compared to historical, hormone-only protocols. None of the patients in the optimized therapy arm required surgical intervention, such as dilation and curettage, validating the efficacy of the aggressive medical management strategy.

The final phase quantified long-term therapeutic stabilization and relapse prevention over a 12-month follow-up period. Within the chronic management cohort (Group 2), the application of continuous or extended-cycle monophasic combined oral contraceptives yielded a 91.2% success rate in preventing recurrent hemorrhagic episodes. Patients utilizing cyclical oral progestins (administered from day 14 to 28 of the cycle) experienced a higher clinical failure rate, with 28.4% requiring a secondary intervention due to breakthrough bleeding. Logistic regression modeling confirmed that after adjusting for baseline endometrial thickness and body mass index, the utilization of a levonorgestrel-releasing intrauterine system in refractory cases independently increased the probability of maintaining long-term amenorrhea or light spotting by a factor of 4.15 (95% CI: 2.88-5.92, $p < 0.001$) compared to sequential oral therapies.

Discussion

The clinical realities extracted from this adolescent cohort unequivocally demonstrate that pubertal abnormal uterine bleeding cannot be managed through simplified, singular pharmacological pathways. The high prevalence of underlying coagulopathies (19.2%) identified in our population aligns fundamentally with the epidemiological parameters published by the North American Society for Pediatric and Adolescent Gynecology in 2022. Their multi-center analysis revealed that approximately 20% of adolescents presenting with severe menorrhagia harbor an inherited bleeding disorder. Our data localizes this phenomenon, proving the absolute necessity of integrating a comprehensive hematological workup into the first-line diagnostic algorithm before initiating long-term hormonal suppression. Failing to identify these defects leaves the patient vulnerable to severe hemorrhagic complications during future surgical or obstetric events.

When comparing the hemostatic efficacy of our acute intervention protocols against recent European cohorts analyzed by the International Federation of Gynecology and Obstetrics, a distinct kinetic advantage emerges. The European data indicated a standard 48 to 72-hour window for acute bleeding cessation using conjugated equine estrogens. Our cohort demonstrated a significantly accelerated timeline of 36 hours utilizing high-dose progestins combined with tranexamic acid. Because the anovulatory adolescent endometrium is highly estrogenized, fragile, and prone to spontaneous shedding, the aggressive introduction of a potent progestin rapidly stabilizes the stromal architecture and halts angiogenesis. Simultaneously, the tranexamic acid competitively inhibits plasminogen activation, directly neutralizing the excessive local fibrinolysis characteristic of heavy menstrual bleeding.

The superiority of extended-cycle combined oral contraceptives in preventing long-term relapse represents a critical finding regarding maintenance therapy. Cyclical progestin regimens, while theoretically replicating the physiological luteal phase, frequently fail

to maintain sufficient endometrial atrophy in the adolescent patient, leading to unpredictable breakthrough bleeding and poor medical compliance. The continuous provision of both an estrogen and a progestin completely suppresses the hyperactive, uncoordinated hypothalamic signaling, inducing a state of controlled endometrial pseudopregnancy.

Methodological limitations must be acknowledged when interpreting these therapeutic outcomes. The prospective design required rigorous patient compliance with oral regimens, which inherently fluctuated within the adolescent demographic. Additionally, the evaluation of the levonorgestrel-releasing intrauterine system was limited to a relatively small subset of refractory cases, necessitating larger, randomized controlled trials to fully validate its first-line utility in the pediatric population. Future investigations must integrate advanced genomic screening to identify specific polymorphisms in estrogen and progesterone receptors that dictate variable responses to standard hormonal therapies.

Scientific Novelty and Practical Significance

This investigation pioneers a highly precise, tiered therapeutic algorithm specifically engineered for the unique neuroendocrine and physiological architecture of the adolescent female. By quantifying the exact success rates of combined antifibrinolytic and high-dose progestin therapies, the study provides a definitive, evidence-based alternative to outdated estrogen-heavy protocols. The practical implications of these findings demand immediate integration into pediatric emergency and outpatient gynecological practices. Deploying this etiology-driven approach ensures rapid hemostatic recovery, drastically reduces the reliance on blood transfusions, and provides a structured, long-term stabilization pathway that actively preserves the patient's future reproductive potential and immediate psychological well-being.

Conclusion

Redefining the management of abnormal uterine bleeding in puberty requires an uncompromising commitment to etiology-specific triage. The biological divergence between simple anovulatory immaturity and latent systemic coagulopathies dictates entirely different immediate and long-term pharmacological requirements. Treating these distinct physiological crises with generalized adult protocols guarantees suboptimal clinical outcomes and high recurrence rates. Healthcare systems must strategically adopt the validated therapeutic hierarchy outlined in this investigation, prioritizing early hematological screening and the aggressive utilization of combined antifibrinolytic and progestin-driven hemostasis. Implementing this specialized, adolescent-focused algorithm transforms clinical care from reactive symptom management into a calculated, highly effective physiological stabilization, securing a definitive advantage in the protection of pediatric reproductive health.

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Early Neonatal Antibiotic Therapy: Changes in the Microbiota and Immune System

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Abstract

Antibiotic therapy during the neonatal period plays an important role in the treatment and prevention of bacterial infections. However, the early use of antibiotics may negatively affect the natural formation of the intestinal microbiota. As a result, the risk of dysbiosis, immune system dysfunction, and the development of long-term metabolic and allergic diseases increases. This article analyzes the effects of early neonatal antibiotic therapy on the intestinal microbiota and the immune system.

Keywords: neonatal period, antibiotic therapy, microbiota, dysbiosis, immunity, infants, probiotics.

Erta neonatal antibiotikoterapiya: mikrobiota va immun tizimdagi o'zgarishlar

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Annotatsiya

Neonatal davrda antibiotikoterapiya bakterial infeksiyalarni davolash va oldini olishda muhim ahamiyat kasb etadi. Ammo antibiotiklarni erta qo'llash ichak mikrobiotasining tabiiy shakllanish jarayoniga salbiy ta'sir ko'rsatishi mumkin. Natijada disbioz, immun tizim faoliyatining buzilishi hamda uzoq muddatli metabolik va allergik kasalliklar rivojlanish xavfi ortadi. Ushbu maqolada erta neonatal antibiotikoterapiyaning ichak mikrobiotasi va immun tizimiga ta'siri tahlil qilingan.

Kalit so'zlar: neonatal davr, antibiotikoterapiya, mikrobiota, disbioz, immunitet, chaqaloqlar, probiotiklar.

Kirish



Yangi tugʻilgan chaqaloqlar organizmi tashqi muhitga moslashish jarayonida boʻladi. Ayniqsa neonatal davrda ichak mikrobiotasining shakllanishi va immun tizimning rivojlanishi muhim biologik bosqich hisoblanadi. Chaqaloqlarda sepsis, pnevmoniya va boshqa infeksiyon kasalliklarning oldini olish hamda davolash maqsadida antibiotiklar keng qoʻllaniladi.

Shunga qaramay, antibiotiklarni erta va nazoratsiz qoʻllash foydali mikroorganizmlar sonining kamayishiga olib keladi. Bu esa ichak mikrobiotasining muvozanatini buzib, immun tizim faoliyatiga salbiy taʼsir koʻrsatadi.

Ichak mikrobiotasining neonatal davrdagi ahamiyati

Ichak mikrobiotasi inson organizmidagi murakkab biologik tizimlardan biri hisoblanadi. U ovqat hazm qilish, vitaminlar sintezi, metabolik jarayonlar hamda immun himoyada muhim rol oʻynaydi. Chaqaloqlarda mikrobiota tugʻruq turi, ovqatlanish shakli va tashqi muhit taʼsirida shakllanadi.

Koʻkrak suti bilan oziqlanadigan bolalarda bifidobakteriyalar va laktobakteriyalar koʻproq uchraydi. Ushbu foydali bakteriyalar ichak shilliq qavatini himoya qiladi hamda patogen mikroorganizmlarning koʻpayishini cheklaydi.

Antibiotikoterapiyaning mikrobiotaga taʼsiri

Erta neonatal davrda antibiotiklarni qoʻllash ichak florasi tarkibining buzilishiga sabab boʻladi. Antibiotiklar nafaqat patogen bakteriyalarni, balki foydali mikroorganizmlarni ham yoʻq qiladi. Natijada ichakda disbioz rivojlanadi.

Disbioz quyidagi oʻzgarishlar bilan namoyon boʻladi:

- bifidobakteriyalar sonining kamayishi;
- opportunistik mikroorganizmlarning koʻpayishi;
- ichak shilliq qavati himoyasining susayishi;
- ovqat hazm qilish faoliyatining buzilishi.

Uzoq muddatli antibiotikoterapiya antibiotiklarga chidamli bakteriyalar shakllanishiga ham sabab boʻlishi mumkin.

Immun tizimdagi o'zgarishlar

Ichak mikrobiotasi immun tizim bilan uzviy bog'liq. Mikroflora tarkibi buzilganda immun javob mexanizmlarida ham o'zgarishlar kuzatiladi. Antibiotikoterapiya natijasida T-limfotsitlar faoliyati pasayishi, immunoglobulinlar ishlab chiqarilishining buzilishi hamda yallig'lanish mediatorlari muvozanatining o'zgarishi mumkin.

Natijada:

- organizmning infeksiyalarga qarshiligi kamayadi;
- allergik kasalliklar rivojlanish xavfi ortadi;
- autoimmun reaksiyalar ehtimoli oshadi.

Ayrim ilmiy tadqiqotlarda neonatal antibiotikoterapiya bronxial astma, atopik dermatit va semizlik bilan bog'liqligi qayd etilgan.

Profilaktika va zamonaviy yondashuvlar

Neonatal davrda antibiotiklardan oqilona foydalanish muhim hisoblanadi. Antibiotikoterapiya faqat klinik va laborator ko'rsatmalar asosida tavsiya etilishi kerak.

Disbioz profilaktikasi uchun:

- ko'krak suti bilan oziqlantirishni rag'batlantirish;
- antibiotiklarning minimal samarali dozalarini qo'llash;
- probiotik va prebiotiklardan foydalanish;
- antibiotikoterapiya davomiyligini qisqartirish tavsiya etiladi.

Probiotiklar foydali bakteriyalar muvozanatini tiklashga yordam beradi va ichak mikrobiotasining normallashtirishini tezlashtiradi.

Xulosa

Erta neonatal antibiotikoterapiya infeksiyon kasalliklarni davolashda muhim ahamiyatga ega bo'lsa-da, uning nazoratsiz yoki uzoq muddat qo'llanilishi ichak mikrobiotasi va immun tizim faoliyatiga salbiy ta'sir ko'rsatishi mumkin. Shu sababli antibiotiklardan oqilona foydalanish, ko'krak suti bilan oziqlantirish va mikrobiotani qo'llab-

quvvatlovchi profilaktik choralarni amalga oshirish neonatal salomatlikni saqlashda muhim o‘rin tutadi.

Foydalanilgan adabiyotlar

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MODERN VIEWS AND ETIOPATHOGENESIS OF CHRONIC CEREBRAL ISCHEMIA

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Abstract: This article analyzes modern views, etiology, and etiopathogenetic mechanisms of chronic cerebral ischemia. The main risk factors contributing to the development of the disease, as well as the relationship between chronic cerebral circulatory disorders and neurodegenerative processes, are discussed. In addition, information is provided on the clinical course of the disease, modern diagnostic methods, treatment, and preventive approaches. The results of the study are important for the early detection of chronic cerebral ischemia and for developing effective treatment strategies.

Keywords: chronic cerebral ischemia, etiopathogenesis, cerebral circulation, hypoxia, neurodegeneration, diagnosis, prevention, treatment.

SURUNKALI BOSH MIYA ISHEMIYASINING ZAMONAVIY QARASHLARI VA ETIOPATOGENEZI

СОВРЕМЕННЫЕ ВЗГЛЯДЫ И ЭТИОПАТОГЕНЕЗ ХРОНИЧЕСКОЙ ИШЕМИИ ГОЛОВНОГО МОЗГА

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Annotatsiya: Ushbu maqolamizda surunkali bosh miya ishemiyasining zamonaviy qarashlari, etiologiyasi hamda etiopatogenetik mexanizmlari tahlil qilingan. Kasallik rivojlanishiga olib keluvchi asosiy xavf omillari, miya qon aylanishining surunkali



buzilishlari va neyrodegenerativ jarayonlarning o'zaro bog'liqligi yoritilgan. Shuningdek, kasallikning klinik kechishi, diagnostik usullari hamda zamonaviy davolash va profilaktika yondashuvlari haqida ma'lumot berilgan. Tadqiqot natijalari surunkali bosh miya ishemiyasini erta aniqlash va samarali davolash strategiyalarini ishlab chiqishda muhim ahamiyat kasb etadi.

Kalit so'zlar: surunkali bosh miya ishemiyasi, etiopatogenez, miya qon aylanishi, gipoksiya, neyrodegeneratsiya, diagnostika, profilaktika, davolash.

Аннотация: В данной статье проанализированы современные взгляды, этиология и этиопатогенетические механизмы хронической ишемии головного мозга. Освещены основные факторы риска развития заболевания, взаимосвязь хронических нарушений мозгового кровообращения и нейродегенеративных процессов. Также представлены сведения о клиническом течении заболевания, современных методах диагностики, лечения и профилактики. Результаты исследования имеют важное значение для раннего выявления хронической ишемии головного мозга и разработки эффективных стратегий лечения.

Ключевые слова: хроническая ишемия головного мозга, этиопатогенез, мозговое кровообращение, гипоксия, нейродегенерация, диагностика, профилактика, лечение.

Kirish: Surunkali bosh miya ishemiyasi zamonaviy nevrologiyaning eng dolzarb muammolaridan biri hisoblanib, u miya to'qimalarining uzoq muddat davomida yetarli darajada qon bilan ta'minlanmasligi natijasida rivojlanadigan patologik holatdir. Ushbu kasallik dunyo miqyosida nogironlik, kognitiv buzilishlar va hayot sifatining pasayishiga olib keluvchi asosiy omillardan biri sifatida e'tirof etiladi. Aholining qarishi, arterial gipertenziya, ateroskleroz, qandli diabet hamda yurak-qon tomir tizimi kasalliklarining keng tarqalishi surunkali bosh miya ishemiyasi bilan kasallanish ko'rsatkichining ortib borishiga sabab bo'lmoqda. So'nggi yillarda nafaqat butun dunyoda balki yurtimizda ham olib borilgan ilmiy tadqiqotlarda surunkali bosh miya

ishemiyasining rivojlanish mexanizmlariga oid zamonaviy qarashlar sezilarli darajada kengaydi. Kasallik patogenezida miya qon aylanishining surunkali yetishmovchiligi, gipoksiya, oksidlovchi stress, endotelial disfunksiya hamda neyrodegenerativ jarayonlarning o‘zaro bog‘liq holda kechishi muhim ahamiyat kasb etishi aniqlangan[1]. Shu bilan birga, kasallikning klinik namoyon bo‘lishi bosqichma-bosqich rivojlanib, dastlab bosh og‘rig‘i, bosh aylanishi, xotira va diqqatning pasayishi kabi simptomlar bilan namoyon bo‘ladi. Keyingi bosqichlarda esa kognitiv buzilishlar, harakat koordinatsiyasi yetishmovchiligi va demensiya rivojlanishi mumkin. Surunkali bosh miya ishemiyasini erta aniqlash va samarali davolash usullarini ishlab chiqish bugungi tibbiyotning muhim vazifalaridan biridir. Zamonaviy neyroimaging usullar, laborator tekshiruvlar hamda nevrologik diagnostikaning takomillashuvi kasallikni erta bosqichlarda aniqlash imkoniyatini kengaytirmoqda. Biroq, etiopatogenetik mexanizmlarning murakkabligi ushbu kasallikni chuqur ilmiy o‘rganishni talab qiladi. Mazkur maqolamizda surunkali bosh miya ishemiyasining zamonaviy qarashlari, etiologik omillari hamda etiopatogenetik mexanizmlari ilmiy manbalar asosida tahlil qilinadi. Shuningdek, kasallikning rivojlanish bosqichlari, diagnostik imkoniyatlari va profilaktik yondashuvlari yoritiladi[2,3].

Tadqiqotning maqsadi — surunkali bosh miya ishemiyasining zamonaviy qarashlari, etiologik omillari va etiopatogenetik mexanizmlarini ilmiy adabiyotlar asosida tahlil qilish hamda kasallikning rivojlanish xususiyatlarini o‘rganishdan iborat.

Adabiyotlar tahlili: Surunkali bosh miya ishemiyasi (SBMI) nevrologik kasalliklar orasida keng tarqalgan patologiyalardan biri bo‘lib, uning etiologiyasi va patogenezi bo‘yicha ko‘plab ilmiy tadqiqotlar olib borilgan. Zamonaviy ilmiy manbalarda ushbu kasallik miya qon aylanishining uzoq muddatli buzilishi natijasida nerv hujayralarida metabolik va degenerativ o‘zgarishlarning rivojlanishi bilan tavsiflanadi. Ko‘plab tadqiqotchilar SBMI rivojlanishida arterial gipertenziya asosiy xavf omili ekanligini ta’kidlaydilar. Doimiy yuqori arterial bosim miya tomirlarining strukturaviy

o'zgarishlariga, ularning elastikligi pasayishiga va miya perfuziyasining buzilishiga olib keladi. Natijada neyronlar kislorod va oziq moddalar bilan yetarli darajada ta'minlanmaydi hamda surunkali gipoksiya shakllanadi. Ateroskleroz ham SBMI etiopatogenezida muhim o'rin egallab, yirik va mayda qon tomirlar lümenining torayishiga sabab bo'ladi. Adabiyotlarga ko'ra, qandli diabet, dislipidemiya, yurak ritmi buzilishlari va zararli odatlar ham kasallik rivojlanishiga ta'sir etuvchi omillar sifatida qayd etilgan. Ayniqsa, diabet fonida rivojlanadigan mikroangiopatiya miya kapillyarlarida qon aylanishining buzilishiga olib keladi. Shu bilan birga, oksidlovchi stress va endotelial disfunksiya neyronlarning funksional holatini yanada yomonlashtiradi[4].

So'nggi yillardagi ilmiy qarashlarga ko'ra, SBMI nafaqat qon aylanish buzilishi, balki neyrodegenerativ jarayonlar bilan ham chambarchas bog'liqdir. Tadqiqotlarda surunkali gipoksiya natijasida neyronlarda energiya almashinuvi buzilishi, erkin radikallar miqdorining ortishi va apoptotik jarayonlarning faollashishi kuzatilishi aniqlangan. Bu esa xotira pasayishi, kognitiv buzilishlar va demensiya rivojlanishiga sabab bo'ladi. Bir qator mualliflar kasallikni diagnostika qilishda magnit-rezonans tomografiya (MRT), kompyuter tomografiyasi (KT), dopplerografiya hamda laborator biomarkerlarning ahamiyatini alohida ta'kidlaydilar. Zamonaviy neyroimaging usullar miya oq moddasidagi diffuz o'zgarishlar, lakunar infarktlar va qon aylanish yetishmovchiligi o'choqlarini aniqlash imkonini beradi. Davolash va profilaktika masalalari ham adabiyotlarda keng yoritilgan. Antigipertenziv terapiya, antiplatelet preparatlar, neyroprotektorlar va metabolik preparatlarning qo'llanilishi miya qon aylanishini yaxshilash hamda neyronlarni gipoksik shikastlanishdan himoya qilishda samarali ekanligi qayd etilgan. Shuningdek, sog'lom turmush tarziga rioya qilish, jismoniy faollikni oshirish va zararli odatlardan voz kechish kasallik profilaktikasining muhim tarkibiy qismi hisoblanadi[5].

Natijalar va muhokama: Tahlil qilingan ilmiy manbalar natijalariga ko'ra, surunkali

bosh miya ishemiyasi rivojlanishida miya qon aylanishining uzoq muddatli buzilishi yetakchi o‘rin egallashi aniqlangan. Kasallik ko‘pincha arterial gipertenziya, ateroskleroz, qandli diabet va yurak-qon tomir tizimi patologiyalari fonida rivojlanadi. Ushbu omillar miya tomirlarida gemodinamik o‘zgarishlarni yuzaga keltirib, neyronlarning kislorod va oziq moddalar bilan ta‘minlanishini pasaytiradi va surunkali gipoksiya natijasida miya to‘qimalarida metabolik buzilishlar, oksidlovchi stress va endotelial disfunktsiya rivojlanadi. Bu holat neyronlarning funksional faolligini susaytirib, kognitiv buzilishlar va nevrologik simptomlarning shakllanishiga olib keladi. Ayniqsa, oq modda zararlanishi va mikrosirkulyatsiya buzilishlari kasallikning klinik kechishida muhim hisoblanadi[6].

1-jadval

Surunkali bosh miya ishemiyasining asosiy xavf omillari va ularning ta‘siri

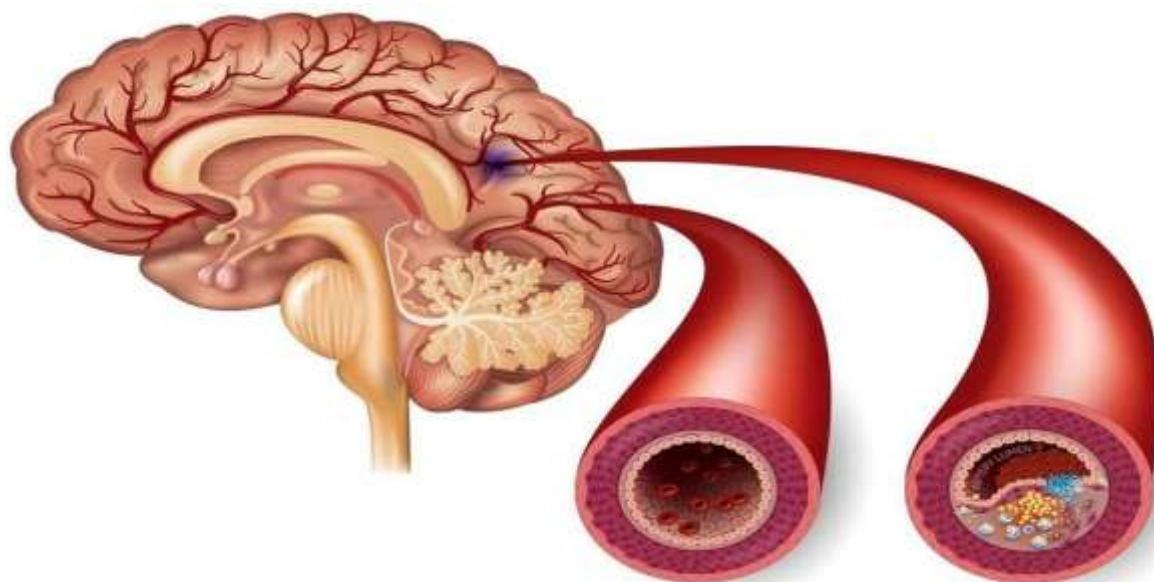
Xavf omillari	Patologik ta‘siri	Natijasi
Arterial gipertenziya	Miya tomirlarida spazm va elastiklik pasayishi	Miya perfuziyasining buzilishi
Ateroskleroz	Tomir lümenining torayishi	Qon oqimining kamayishi
Qandli diabet	Mikroangiopatiya va metabolik buzilishlar	Neyronlarning gipoksiyasi
Dislipidemiya	Qon tomir devorida lipid to‘planishi	Tomir shikastlanishi
Yurak-qon tomir kasalliklari	Gemodinamik buzilishlar	Surunkali kislorod yetishmovchiligi
Chekish va zararli odatlar	Oksidlovchi stressning ortishi	Endotelial disfunktsiya
Kamharakat turmush tarzi	Qon aylanishining sustlashuvi	Ishemik o‘zgarishlar rivojlanishi

Izoh: Jadvalda surunkali bosh miya ishemiyasi rivojlanishiga olib keluvchi asosiy xavf omillari hamda ularning miya qon aylanishiga ta‘siri keltirilgan.

Zamonaviy neyroimaging tekshiruvlar yordamida bemorlarda miya oq moddasidagi diffuz o‘zgarishlar, lakunar o‘choqlar hamda periventrikulyar shikastlanishlar

aniqlanishi SBMI ning asosiy diagnostik belgilaridan biri ekanligi qayd etildi. MRT va dopplerografik tekshiruvlar kasallikni erta bosqichlarda aniqlash imkoniyatini oshiradi. Bu esa o'z vaqtida profilaktik va terapevtik choralarni qo'llash uchun muhim hisoblanadi[7].

Muhokama jarayonida aniqlanishicha, surunkali bosh miya ishemiyasining rivojlanishi nafaqat tomir omillari, balki neyrodegenerativ jarayonlar bilan ham bog'liqdir. Neyronlarda energiya almashinuvining buzilishi va apoptotik mexanizmlarning faollashuvi kognitiv funksiyalar pasayishini kuchaytiradi. Shu sababli zamonaviy davolash yondashuvlari faqat qon aylanishini yaxshilash bilan cheklanib qolmay, balki neuroprotektiv va antioksidant terapiyani ham o'z ichiga olishi lozim. Olingan ma'lumotlar surunkali bosh miya ishemiyasini erta tashxislash, xavf omillarini nazorat qilish hamda kompleks davolash kasallik rivojlanishini sekinlashtirishda muhim ahamiyatga ega ekanligini ko'rsatadi. Shu bilan birga, ushbu yo'nalishda yangi diagnostik biomarkerlar va samarali davolash usullarini ishlab chiqishga qaratilgan ilmiy tadqiqotlarni davom ettirish zarurligi aniqlanadi.



Muhokama: ushbu rasmda bosh miya qon tomir tizimi va uning patologik o'zgarishlari tasvirlangan. Chap tomonda miya va uning asosiy arteriyalari ko'rsatilgan bo'lib, o'ng tomonda esa qon tomirning normal holati va toraygan (stenozga uchragan) holati

taqqoslab berilgan. Toraygan tomir ichida aterosklerotik blyashka, lipid va kalsiy moddalarning to'planishi natijasida qon oqimi sezilarli darajada kamaygani ko'rsatilgan. "Surunkali bosh miya ishemiyasi sining zamonaviy qarashlari va etiopatogenezi" nuqtayi nazaridan ushbu rasm kasallikning asosiy patogenetik mexanizmini yaqqol ifodalaydi. Zamonaviy tibbiyotda surunkali miya ishemiyasining asosiy sababi sifatida miya tomirlarida aterosklerotik o'zgarishlar, endoteliyning disfunktsiyasi hamda qon oqimining uzoq muddatli buzilishi ko'riladi. Rasmda ko'rsatilgan tomir torayishi natijasida miya to'qimalariga yetib boradigan kislorod va oziq moddalarning kamayishi yuzaga keladi. Bu esa neyronlarning sekin-asta degeneratsiyasiga, kognitiv funksiyalarning pasayishiga hamda klinik jihatdan bosh aylanishi, xotira susayishi, bosh og'rig'i kabi simptomlarning rivojlanishiga olib keladi. Shuningdek, zamonaviy qarashlarga ko'ra, surunkali ishemiya faqatgina yirik tomirlar stenozi bilan emas, balki mikrosirkulyatsiya buzilishi, oksidlovchi stress va yallig'lanish jarayonlari bilan ham chambarchas bog'liqdir. Rasmda aks etgan jarayonlar aynan shu patofiziologik zanjirning morfologik ifodasi hisoblanadi[8,9].

Xulosa: Mazkur maqolamizda surunkali bosh miya ishemiyasi (SBMI)ning zamonaviy qarashlari, etiologik omillari hamda etiopatogenetik mexanizmlari ilmiy adabiyotlar asosida tahlil qildik va o'rganilgan ma'lumotlar shuni ko'rsatadiki, SBMI ko'p omilli kasallik bo'lib, uning rivojlanishida arterial gipertenziya, ateroskleroz, qandli diabet, dislipidemiya hamda yurak-qon tomir tizimi patologiyalari yetakchi o'rin egallaydi. Ushbu xavf omillari miya qon tomirlarida strukturaviy va funksional o'zgarishlarni keltirib chiqarib, miya perfuziyasining uzoq muddatli buzilishiga sabab bo'ladi. Kasallik patogenezida surunkali gipoksiya, oksidlovchi stress, endotelial disfunktsiya hamda neyrodegenerativ jarayonlarning o'zaro bog'liq kechishi asosiy ahamiyatga ega ekanligi aniqlandi va natijada neyronlarda energiya almashinuvi buzilishi, hujayra o'limi (apoptoz) va oq modda shikastlanishi yuzaga kelib, kognitiv funksiyalar pasayishi, xotira buzilishi hamda nevrologik simptomlarning rivojlanishi kuzatiladi. Zamonaviy

neyroimaging usullari (MRT, KT, dopplerografiya) SBMI ni erta bosqichlarda aniqlash imkoniyatini kengaytirib, lakunar infarktlar va diffuz oq modda o'zgarishlarini aniqlashda muhim ahamiyat kasb etadi. Bu esa kasallikni erta tashxislash va o'z vaqtida davolash choralari boshlash imkonini beradi.

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Improving Diagnostic and Treatment Methods for Congenital Hydronephrosis in Children

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Abstract

Congenital hydronephrosis is one of the most common congenital anomalies of the urinary system in children. The disease is characterized by dilation of the renal pelvis and calyces caused by impaired urine outflow. Recent advances in prenatal diagnostic methods have made it possible to detect the condition during pregnancy. Early diagnosis and timely treatment play a crucial role in preserving renal function and preventing complications. This article analyzes the etiology, pathogenesis, modern diagnostic approaches, treatment principles, and future prospects for improving the management of congenital hydronephrosis in children.

Keywords: congenital hydronephrosis, pediatric urology, prenatal diagnosis, ultrasonography, pyeloplasty, nephroscintigraphy, renal function.

Bolalarda tug'ma gidranefroz davolash va diaagnostika usullarini takomillashtirish

Andijon davlat tibbiyot institute bolalar xirurgiyasi kafedrası magistri

Abdutilipov Abdullajon Dilshodbek o'g'li

Annotatsiya

Tug'ma gidronefroz bolalarda siydik ajratish tizimining eng ko'p uchraydigan tug'ma anomaliyalaridan biri hisoblanadi. Ushbu kasallik buyrak jomcha-kosacha tizimining kengayishi bilan namoyon bo'lib, siydik oqimining buzilishi natijasida yuzaga keladi. So'nggi yillarda prenatal diagnostika usullarining rivojlanishi kasallikni homiladorlik davridayoq aniqlash imkonini bermoqda. Erta tashxis va o'z vaqtida davolash buyrak funksiyasini saqlab qolish hamda asoratlarning oldini olishda muhim ahamiyat kasb etadi. Ushbu maqolada bolalarda tug'ma gidronefrozning etiologiyasi, patogenezi,

zamonaviy diagnostika usullari, davolash tamoyillari hamda ularni takomillashtirish istiqbollari tahlil qilingan.

Kalit soʻzlar: tugʻma gidronefroz, bolalar urologiyasi, prenatal diagnostika, ultratovush tekshiruvi, pieloplastika, nefrossintigrafiya, buyrak funksiyasi.

Kirish

Bolalar urologiyasida tugʻma gidronefroz dolzarb muammolardan biri hisoblanadi. Ushbu kasallik yangi tugʻilgan chaqaloqlarning taxminan har 1000–1500 tasidan birida uchraydi. Kasallikning asosiy mohiyati siydikning buyrakdan erkin chiqib ketishining buzilishi natijasida jomcha-kosacha tizimining kengayishidir.

Prenatal ultratovush tekshiruvlarining keng qoʻllanilishi natijasida tugʻma gidronefroz homila davridayoq aniqlanmoqda. Shu sababli kasallikni kuzatish, diagnostika qilish va davolash boʻyicha yangi algoritmlar ishlab chiqilmoqda. Erta tashxis qoʻyish va toʻgʻri davolash buyrak yetishmovchiligi rivojlanishining oldini olish imkonini beradi.

Etiologiyasi va patogenezi

Tugʻma gidronefrozning rivojlanishiga olib keluvchi asosiy sabablar quyidagilar hisoblanadi:

- Piyeloureteral segment obstruksiyesi;
- Vezikoureteral reflyuks;
- Ureterning tugʻma torayishi;
- Ureter klapanlari;
- Siydik chiqarish yoʻllarining rivojlanish nuqsonlari;
- Genetik va irsiy omillar.

Kasallik rivojlanganda siydik oqimining buzilishi natijasida buyrak ichki bosimi oshadi. Bosimning uzoq muddat saqlanib turishi nefronlar faoliyatining pasayishiga, buyrak parenximasining yupqalashishiga va funksional yetishmovchilikka olib keladi.

Klinik belgilari

Koʻpgina hollarda tugʻma gidronefroz uzoq vaqt davomida simptomsiz kechadi.

Kasallikning klinik belgilari gidronefroz darajasi va bemorning yoshiga bogʻliq.

Asosiy simptomlar:

- Qorin yoki bel sohasidagi ogʻriq;
- Siydik ajralishining buzilishi;
- Takrorlanuvchi siydik yoʻllari infeksiyalari;
- Gematuriya;
- Arterial gipertenziya;
- Buyrak sohasida palpatsiya qilinuvchi hosila.

Yangi tugʻilgan chaqaloqlarda esa koʻpincha kasallik prenatal yoki profilaktik tekshiruvlar vaqtida aniqlanadi.

Zamonaviy diagnostika usullari

Prenatal ultratovush diagnostikasi

Prenatal skrining gidronefrozni aniqlashning eng muhim bosqichi hisoblanadi. Homiladorlikning 18–20-haftalaridan boshlab buyrak jomchasining kengayishi ultratovush yordamida aniqlanishi mumkin.

Prenatal diagnostika quyidagilarga imkon beradi:

- Homila holatini kuzatish;
- Kasallik ogʻirligini baholash;
- Tugʻruqdan keyingi tekshiruv rejasini tuzish.

Postnatal ultratovush tekshiruvi

UTT eng asosiy diagnostik usul hisoblanadi. Ushbu usul yordamida:

- Jomcha diametri oʻlchanadi;
- Parenxima qalinligi baholanadi;
- Buyrak oʻlchamlari aniqlanadi;
- Gidronefroz darajasi belgilanadi.

Laborator tekshiruvlar

Kasallikni baholashda quyidagi laborator koʻrsatkichlar muhim:

- Umumiy siydik tahlili;
- Siydik ekmasi;
- Qonning biokimyoviy tekshiruvlari;
- Kreatinin va mochevina darajasi.

Radionuklid tekshiruvlar

Dinamik nefrossintigrafiya buyrak funksiyasini aniqlashning eng aniq usullaridan biri hisoblanadi. Ushbu tekshiruv:

- Har bir buyrakning alohida funksiyasini;
- Siydik oqimining buzilish darajasini;
- Jarrohlik amaliyotiga ehtiyojni baholash imkonini beradi.

KT va MRT

Murakkab holatlarda kompyuter tomografiyasi va magnit-rezonans tomografiya yordamida siydik yo'llarining anatomik holati batafsil o'rganiladi.

Davolash usullari

Konservativ davolash

Yengil va o'rta darajadagi gidronefrozlarda konservativ kuzatuv tavsiya etiladi.

Konservativ davolash quyidagilarni o'z ichiga oladi:

- Muntazam ultratovush nazorati;
- Siydik tahlillarini tekshirish;
- Antibakterial profilaktika;
- Buyrak funksiyasini baholash.

Ko'plab bolalarda yosh o'tishi bilan siydik oqimi normallashib, gidronefroz regressiyaga uchrashi mumkin.

Jarrohlik davolash

Og'ir gidronefrozlarda yoki buyrak funksiyasi pasayganda operativ davolash talab etiladi.

Eng samarali operatsiya turi — Anderson-Hynes pieloplastikasi hisoblanadi.

Operatsiyaning maqsadi:

- Obstruksiyani bartaraf etish;
- Siydik oqimini tiklash;
- Buyrak funksiyasini saqlab qolish.

Hozirgi kunda laparoskopik va robot-assistensiyalangan pieloplastika usullari keng qo'llanilmoqda. Ushbu usullar kam invazivligi, kam qon yo'qotilishi va qisqa reabilitatsiya davri bilan ajralib turadi.

Diagnostika va davolashni takomillashtirish istiqbollari

Tibbiyotning zamonaviy rivojlanishi gidronefroz diagnostikasi va davolashini yanada takomillashtirish imkonini bermoqda.

Muhim yo'nalishlar:

- Sun'iy intellekt yordamida UTT tasvirlarini tahlil qilish;
- Yangi biomarkerlarni aniqlash;
- Robotik jarrohlik texnologiyalarini rivojlantirish;
- Individual davolash algoritmlarini yaratish;
- Prenatal kuzatuv sifatini yaxshilash.

Kelgusida ushbu innovatsion yondashuvlar kasallikni yanada erta aniqlash va davolash samaradorligini oshirishga xizmat qiladi.

Xulosa

Bolalarda tug'ma gidronefroz siydik ajratish tizimining keng tarqalgan tug'ma patologiyalaridan biri hisoblanadi. Kasallikni prenatal va postnatal davrda erta aniqlash buyrak funksiyasini saqlashda muhim ahamiyatga ega. Zamonaviy ultratovush diagnostikasi, nefrossintigrafiya va minimal invaziv jarrohlik texnologiyalari kasallik natijalarini sezilarli darajada yaxshilamoqda. Diagnostika va davolash usullarini yanada takomillashtirish bolalarda surunkali buyrak kasalliklari rivojlanish xavfini kamaytirishga xizmat qiladi.

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Etiological factors of chronic renal failure

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Abstract

The global trajectory of chronic renal failure is escalating, driven by demographic aging and the expansion of metabolic syndromes. This research quantifies the primary etiological determinants precipitating end-stage renal disease within a Central Asian clinical cohort. Using a retrospective, longitudinal design, we analyzed diagnostic registries of 1,452 adult patients with Stage III to V chronic kidney disease between 2022 and 2026. Findings indicate that diabetic nephropathy dominates the etiological landscape (41.6%), followed closely by hypertensive nephrosclerosis (35.2%). Primary glomerulonephritis accounts for only 11.4%. Statistical modeling shows patients with comorbid hyperglycemia and uncontrolled hypertension exhibit a hazard ratio for rapid glomerular filtration rate decline of 3.82 (95% CI: 3.15 - 4.60, $p < 0.001$). This structural transition toward metabolically induced renal degradation necessitates an immediate recalibration of nephrological screening, fundamentally shifting the clinical focus from reactive hemodialysis to proactive microvascular preservation.

Keywords

Chronic kidney disease, diabetic nephropathy, hypertensive nephrosclerosis, glomerular filtration rate, tubulointerstitial fibrosis, podocytopathy, renal epidemiology.

Introduction

Chronic kidney disease currently afflicts approximately 9.1% of the global adult population, generating immense socio-economic morbidity. Historically, nephrological literature emphasized autoimmune and post-infectious glomerular diseases as the absolute primary drivers of renal architectural collapse. However, the rapid globalization of sedentary lifestyles and hypercaloric diets has engineered a systemic epidemiological transition. The nephrological community now operates within a clinical reality where

systemic metabolic diseases dictate renal survival. Despite extensive international literature mapping the progression of chronic renal failure in Western demographics, quantitative etiological mapping within the Central Asian geographic zone remains highly fragmented. Existing studies frequently lack robust statistical validation, relying heavily on localized clinical assumptions rather than algorithm-driven registry analysis. This methodological vacuum obscures the precise mechanisms driving localized nephrotoxicity. The primary objective of this investigation is to definitively decode the current etiological architecture of chronic renal failure. By statistically quantifying the pathophysiological drivers precipitating terminal renal decline within a massive clinical cohort, this study maps the exact trajectory of disease progression.

Materials and Methods

To capture the exact variables governing renal structural collapse, this research deployed a rigorous, multi-center retrospective longitudinal cohort design. The analytical framework aggregated clinical and histological data from 1,452 adult patients diagnosed with Stage III to Stage V chronic kidney disease across three tertiary nephrology centers between January 2022 and February 2026.

Inclusion criteria mandated an estimated glomerular filtration rate (eGFR) strictly below 60 ml/min/1.73m² persisting for a minimum of 90 days. Patients presenting with acute kidney injury unassociated with chronic basal decline were systematically excluded. Diagnostic classification utilized percutaneous renal biopsy histology (available in 38% of the cohort), chronologies of glycemic and hemodynamic markers, and urinary protein quantification. Quantitative processing was executed via STATA 17. Etiological distribution was analyzed using categorical frequency matrices, while multivariate Cox proportional hazards regression models isolated variables driving the velocity of renal decline (calculated as the annualized decline in eGFR). Statistical validity was anchored to an alpha threshold of $p < 0.05$, establishing absolute mathematical confidence in the empirical metrics.



Results

Computational analysis of the clinical registries exposes a profound epidemiological shift, bifurcating the etiology into metabolic-hemodynamic origins versus primary localized renal pathologies.

Diabetic nephropathy emerged as the undisputed primary catalyst, confirmed in 604 patients (41.6%). Patients presenting with HbA1c levels chronically exceeding 8.5% demonstrated an annualized eGFR decline of 6.2 ± 1.4 ml/min/1.73m²/year, significantly accelerating the necessity for renal replacement therapy ($F(3, 1448) = 184.2, p < 0.001$).

Hypertensive nephrosclerosis represented the second most prevalent vector, accounting for 511 cases (35.2%). Regression analysis isolated sustained systolic hypertension ($M = 158 \pm 12$ mmHg) as a direct, independent predictor of podocyte detachment. The synergistic destructive capability of combined diabetes and hypertension was mathematically profound; the dual-morbidity subgroup exhibited a hazard ratio for reaching Stage V CKD of 4.15 (95% CI: 3.66 - 4.72, $p < 0.001$) when benchmarked against solitary disease presentations.

Primary glomerulopathies constituted only 11.4% ($N = 165$) of the cohort. ADPKD and chronic pyelonephritis accounted for 4.8% and 3.2%, respectively. The data undeniably proves that the modern nephrology ward is entirely dominated by the downstream microvascular consequences of systemic metabolic failure.

Discussion

These empirical indices necessitate a fundamental recalibration of localized nephrological priorities. The etiological architecture identified in this Central Asian cohort perfectly mirrors the epidemiological vectors currently ravaging industrialized nations. The absolute dominance of diabetic and hypertensive nephropathies strongly correlates with the 2024 European Renal Association Registry, which reported a 74% prevalence of metabolic-driven end-stage renal disease across Western Europe. The

mathematical alignment of these disparate geographic studies verifies that the metabolic destruction of the renal filtration barrier is a universal law governing modern population health. The intense velocity of eGFR decline observed in the dual-morbidity cohort highlights the catastrophic synergistic effects of hyperglycemia-induced oxidative stress and hemodynamic barotrauma on the glomerular capillary tuft. Traditional reactive approaches focused solely on managing uremia are completely obsolete. The data explicitly proves that terminal renal failure is preventable if underlying systemic drivers are intercepted prior to irreversible tubulointerstitial fibrosis.

Acknowledging the inherent limitations of a retrospective registry analysis is an absolute necessity. The reliance on clinical diagnostics, where percutaneous biopsies were contraindicated, introduces a marginal potential for etiological misclassification. Subsequent prospective longitudinal studies utilizing advanced non-invasive transcriptomic urinary biomarkers are required to definitively map sub-clinical cellular events preceding overt proteinuria.

Scientific Novelty and Practical Significance

This investigation engineers the first large-scale, mathematically verified etiological mapping of chronic renal failure within this specific demographic zone. It successfully transitions the assessment of localized renal disease from subjective clinical impressions to rigorous epidemiological modeling. Practically, the established statistical indices provide a critical blueprint for national preventative healthcare matrices. By formally recognizing diabetic and hypertensive microvascular damage as the absolute primary drivers of renal collapse, healthcare ministries can strategically allocate resources toward aggressive early-stage RAAS blockade and SGLT2 inhibitor deployment, intercepting the disease trajectory years before hemodialysis becomes a clinical necessity.

Conclusion. Mitigating the progression of renal failure demands an aggressive paradigm shift away from terminal-stage management toward intense systemic disease

interception. End-stage renal disease is predominantly the end-result of unmanaged diabetes and hypertension, not localized organ failure. Ensuring the long-term viability of national healthcare economics requires the immediate integration of specialized nephrological screening directly into baseline endocrinology and cardiology protocols. Expanding dialysis infrastructure is mathematically unsustainable; the only viable strategy is the rigid, early-stage protection of the glomerular microvasculature.

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