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KASALLIKLARGA TASHXIS QO'YISHDA pH DAN FOYDALANISH

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Kalit so'zlar: pH muvozanati (gomeostazi); hujayradan tashqari atsidoz; elektrokimyoviy sensor; optik sensor; ^{31}P-MRS; acidoCEST MRT; giperpolyarizatsiyalangan MRT; o'sma mikromuhiti; saraton diagnostikasi; pHga sezgir dori tashuvchi.

Annotatsiya

Maqsad. Organ va to'qimalarda pHni o'lchash texnologiyalari, mahalliy va tizimli kislota-asos o'zgarishlarining kasalliklar bilan bog'liqligi hamda saraton diagnostikasi va davolashdagi amaliy imkoniyatlarini baholash.

Usullar. 2016–2026 yillardagi ishlarga ustuvorlik berilgan maqsadli adabiyot qidiruvi, fundamental manbalar, DOI bo'yicha bibliografik tekshiruv va birlamchi matnlardan dalillar ajratishga asoslangan narrativ sintez bajarildi. 2026 yil 1 noyabrgacha tekshirilgan korpus 163 noyob maqolani qamrab oldi. Europe PMC/PubMed bilan bog'langan manbalar, Crossref, nashriyot va elektron ilmiy manbalar ko'rib chiqildi; Consensus yordamchi qidiruv va manba bo'limlarini aniqlashtirish uchun ishlatildi. Hujayra ichi, hujayradan tashqari, organella, bo'shliq va biologik suyuqlik pHlari alohida tahlil qilindi. Umumiy sharhga 2016 yil 1 yanvardan 2026 yil 3 noyabrgacha chop etilgan inson tadqiqotlarida ekzogen CEST-MRT orqali o'sma pH_esini miqdoriy baholashga bag'ishlangan sistematik modul qo'shildi.

Natijalar. To'liq matni yoki to'liq matn sahifasi tasdiqlanib, tegishli bo'limlari tekshirilgan manbalar soni 90 taga yetdi. Qolgan manbalarda annotatsiya, tanlangan bo'lim parchalari yoki preprint bilan cheklanish ochiq qayd etildi. Elektrokimyoviy va optik sensorlar mahalliy uzluksiz o'lchovga, ^{31}P-MRS va CEST esa fazoviy tasvirlashga imkon beradi; ularning ko'rsatkichlari bir-birini to'liq almashtirmaydi. Saraton atsidozi metabolik, immun va membrana jarayonlari bilan bog'liq, biroq klinik diagnostik tadqiqotlar tekshirilganlar soni kamligi, zondning to'qimaga bir tekis tarqalmasligi va taqqoslash uchun ishonchli mustaqil usul (referens) yetishmasligi bilan cheklangan. pHga ta'sir qilishga asoslangan o'smaga qarshi yondashuvlarning katta qismi hali hayvon va hujayra tajribalari (preklinik) yoki dastlabki klinik sinov bosqichida. Kislota-asos muvozanatiga ta'sir qiluvchi davolashda qon biokimyoviy ko'rsatkichlarini me'yorlashtirish ayrim klinik natijalarni yaxshilashi mumkin, ammo bemorlarning tirik qolishi bo'yicha foyda izchil tasdiqlanmagan. Sistematik modulda 83 noyob yozuv saralanib, ikki klinik hisobot kiritildi. Ular pH_e xaritalashning texnik imkoniyati va diagnostik biomarker sifatidagi istiqbolini ko'rsatdi; bemor darajasidagi sezgirlik va spetsifiklikni baholash uchun ma'lumot yetarli emas edi.

Xulosa. pHning klinik qiymati uning qaysi biologik muhitda (hujayra ichi, hujayra tashqarisi, organ bo'shlig'i) o'lchanishiga, makon va vaqt bo'yicha o'zgarishiga hamda o'lchovning aniq kalibrlanishiga bog'liq. Eng istiqbolli yo'nalishlar – aynan o'lchanayotgan muhitga xos monitoring, mustaqil taqqoslash usuliga (referensga) ega ko'p markazli diagnostik tekshiruvlar va biomarker o'zgarishini bemor uchun muhim natijalar bilan bog'laydigan sinovlardir.

Havola uchun

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1 Kirish

Proton faolligi fermentativ reaksiyalar, membrana transporti va oqsil signallariga ta'sir qiladi. Klinikada kislota-asos holati odatda qon ko'rsatkichlari bilan baholanadi. Biroq interstitsial suyuqlik, sitozol va organellalar atrofidagi mikromuhitda boshqa sharoit shakllanishi mumkin. Saraton hujayrasida tashqi muhitning kislotalanishi bilan ichki pHning nisbatan ishqoriy saqlanishi buning yaxshi o'rganilgan misolidir [1, 2, 3]. Mahalliy pHning makon va vaqt bo'yicha kuzatuvi metabolizm haqida axborot beradi; signalning muayyan kasallikka xosligi esa alohida tekshiriladi.

So'nggi o'n yillikdagi yutuqlar protonlarga sezgir elektrod va optik materiallarni kichraytirish hamda barqarorlashtirish [4, 5, 6], CEST, ^{31}P-spektroskopiya va giperpolyarizatsiyalangan substratlar orqali tasvirlash [7, 8, 9, 10], shuningdek, o'sma kislotaliligidan zondni faollashtirish, dori chiqarilishini boshqarish va davolash nishoni sifatida foydalanish bilan bog'liq [11, 12, 13, 14, 15, 16, 17, 18]. Fantomdagi analitik sezgirlik, hayvondagi biologik javob va bemordagi klinik foyda ushbu rivojlanishning turli bosqichlaridir.

Tadqiqotlarni qiyoslashda usullar turli biologik muhitlarni o'lchashi va turli validatsiya mezonlariga tayanishi hisobga olinadi. Ekzogen CEST bilan baholangan o'sma pH_esi endogen amin-CEST signali yoki pH_iga sezgir ^{31}P-MRS bilan bir xil kattalik emas [10, 19]. Voksel, to'qima kesimi yoki hujayralarni mustaqil bemor sifatida sanash dalil aniqligini oshirib ko'rsatadi [8, 18, 20]. Davolashda pH yoki HCO_3^- siljishi ham o'sma nazorati, jismoniy funksiya va o'lim ko'rsatkichlariga doim mos kelmaydi [21, 22, 23, 24].

Sharhda pHni o'lchash usullarining analitik xususiyatlari qiyoslanadi, organlarga xos patologik o'zgarishlar biologik sharoit bilan bog'lanadi va onkologik qo'llanishning klinik darajasi baholanadi. Bunda o'lchangan muhit, kalibrlash va referens, mustaqil kohortadagi takroriy tasdiq hamda aralashuvning klinik natijaga ta'siri asosiy mezon sifatida olindi.

2 Adabiyotlarni izlash va sintez metodologiyasi

Asosiy qidiruv davri 2016 yil 1 yanvar — 2026 yil 1 noyabr etib belgilandi; oldingi fundamental ishlar alohida kiritildi. Europe PMCdagi 32 maqsadli so'rov 857 yozuv berdi. Aynan takror 52 yozuv chiqarilgach, 805 noyob nomzod qoldi. Usul, organ va onkologik yo'nalishlarni qamragan 163 jurnal maqolasi tanlandi. Ulardan 78 tasi 2024–2026 yillarda, beshtasi 2016 yilgacha chop etilgan. Bu keng korpus uchun qidiruv natijalarining barcha sahifalari olinmagani sababli umumiy qism narrativ sharh sifatida saqlandi. Qidiruvi va mezonlari alohida hujjatlashtirilgan sistematik modul butun korpusni sistematik sharhga aylantirmaydi.

Qidiruv bloklarida "hydrogen-ion concentration/pH", "intracellular/extracellular", organ va kasallik nomlari hamda "sensor", "fluorescence", "magnetic resonance spectroscopy", "CEST", "hyperpolarized", "tumor microenvironment", "diagnosis" va "therapy" terminlari mantiqiy (Boolean) operatorlar bilan birlashtirildi. PubMed bilan bog'langan Europe PMC manbalari va annotatsiyalar ko'rib chiqildi. Har bir DOI, sarlavha, muallif va jurnal Crossref bilan solishtirildi. Scopus va Web of Science bazalarida bevosita qidiruv bajarilmadi.

Organ yoki biologik muhitda pHni o'lchagan, pHga sezgir signalni metodologik tekshirgan, pHga bog'liq kasallik mexanizmini baholagan yoki tegishli aralashuvni sinagan original ishlar kiritildi. Nazariy asos va umumiy kontekst uchun metodologik maqola, klinik konsensus, sharh va metatahlillar ham qo'llandi. Mavzuga bevosita aloqasiz manbalar, aynan takror nashrlar va bibliografik mosligi tasdiqlanmagan materiallar dalil sifatida ishlatilmadi. Hujayra, hayvon, inson, in silico va ikkilamchi sintez dizaynlari ajratildi.

Dastlab 29 manbaning to‘liq matnidagi tegishli bo‘limlar tekshirildi. Qolgan 134 DOI uchun nashriyot va elektron ilmiy manba havolalari, Europe PMC ochiq XML matnlari, Crossref metama’lumotlari va OpenAlexdagi joylashuv manbalari izlandi. Ulardan 59 tasining to‘liq nusxasi olindi, yana bir manbaning to‘liq matn sahifasidagi tegishli bo‘limlar tekshirildi. 73 manbaning yakuniy to‘liq matni olinmadi; yana birida faqat preprint topildi. Qo‘shimcha sistematik tahlilda [32] manbaning to‘liq matnidagi klinik metod va natijalar ham tekshirildi. Shundan keyin asosiy 163 manbaning kirish holati quyidagicha yangilandi: 90 manba – to‘liq matnning tegishli bo‘limlari; 69 manba – annotatsiya; uch manba – annotatsiya va tanlangan bo‘lim parchalari; bir manba – annotatsiya va preprint. To‘liq nusxani olish uning barcha qo‘shimcha materiallari ham o‘qilganini anglatmaydi.

Consensus yordamchi qidiruv va manbalarning tegishli bo‘limlarini aniqlashtirish uchun ishlatildi. Xizmatning sintezi va qaytargan parchalari alohida saqlandi. Uning 100 manbali natijasi 134 DOI bo‘yicha tugallangan tekshiruv yoki 100 yangi mustaqil tadqiqot deb hisoblanmadi. Birlamchi to‘liq matni olinmagan manbalarning metod yoki natija parchalari to‘liq matn o‘qildi deb belgilanmadi. Bibliografiyada F tegishli to‘liq matn bo‘limlari, C annotatsiya va tanlangan parchalar, A annotatsiya, A/P esa annotatsiya va yakuniy nashrga tengligi to‘liq tasdiqlanmagan preprintni bildiradi. Bu belgilar tadqiqot sifatini emas, foydalanilgan matn hajmini ko‘rsatadi.

Natijalar biologik muhit, texnologiya, kalibrlash diapazoni, mustaqil namuna birligi, nazorat va yakuniy ko‘rsatkich bo‘yicha qiyoslandi. Original natijalar imkon qadar birlamchi maqolalardan olindi; metatahlil va guruhosti qayta tahlillari dastlabki kohortalar bilan bog‘landi. Keng korpus RoB 2 yoki SYRCLE bilan rasmiy baholanmadi. Diagnostik modulda QUADAS-3ning qo‘llanish shartlari tekshirilib, biomarker farqi uchun GRADE domenlariga tayangan moslashtirilgan profil tuzildi. Ikki mustaqil inson mutaxassis alohida saralash o‘tkazmagan. Assotsiatsiya sababiyatdan, statistik ahamiyat klinik ahamiyatdan ajratildi. Yangi metatahlil uchun individual ma’lumot yo‘qligi emas, birlashtirishga yaroqli mustaqil klinik baholar yetishmasligi asosiy to‘siq bo‘ldi.

Qisqartmalar. MRT — magnit-rezonans tomografiya; MRS — magnit-rezonans spektroskopiya; MRST — magnit-rezonans spektroskopik tasvirlash; CEST — kimyoviy almashinish orqali to‘yinishni uzatish; APT — amid protonlari uzatilishiga sezgir tasvirlash; RMSE — o‘rtacha kvadratik xatoning kvadrat ildizi; MAE — o‘rtacha mutlaq xato; ROI — tadqiqot sohasi; HCM — gipertrofik kardiomiopatiya; DOY — diabetik oyoq yarasi; HNSCC — bosh va bo‘yin yassi hujayrali saratoni; RRT — buyrak o‘rnini bosuvchi terapiya; IPD — individual ishtirokchi ma’lumotlari; eGFR — hisoblangan glomerulyar filtratsiya tezligi; AUC — ROC egri chizig‘i ostidagi yuza; ASL — nafas yo‘li yuzasidagi suyuqlik.

2.1 Sistematik modulning savoli va mezonlari

Sistematik savol katta yoshli insonlarda qattiq o‘smalarning hujayradan tashqari pHini yodli ekzogen agentli CEST-MRT bilan xaritalash xavfli va yaxshi sifatli o‘choqlarni farqlash uchun qanday dalil berishini aniqlashga qaratildi. Asosiy yakun — mustaqil referens tashxisga nisbatan bemor darajasidagi diagnostik aniqlik. Qo‘shimcha yakunlar sifatida pH_ening guruhlararo farqi, texnik bajarilish va talqin qilib bo‘lmaydigan o‘lchovlar olindi. Gistologik yoki klinik referens kasallikni tasdiqlashi mumkin, ammo pH o‘lchovining analitik to‘g‘riligini mustaqil tasdiqlamaydi.

Original klinik hisobotda tirik insonning qattiq o‘smasi uchun pH_e sonli bahosi yoki shunday bahoni olishga urinish natijasi berilishi talab qilindi. Nazorat guruhining yo‘qligi texnik bajarilish sintezidan chiqarish sababi bo‘lmadi. Faqat hayvon, hujayra yoki fantom ma’lumotlari, noonkologik tekshiruvlar, sharh va metodik boblar, natijasiz protokollar hamda mutlaq pH_ega aylantirilmagan endogen APT/amin-CEST ko‘rsatkichlari chiqarildi. Shu bois bu modul ^{31}P-MRS, deepCEST yoki pH-faollashuvchi jarrohlik fluoressensiyasining barcha klinik dalillarini qamramaydi; ular umumiy sharhda saqlandi.

2.2 Qidiruv va baholash tartibi

Qidiruv 2026 yil 3 noyabrda Europe PMC indeksida, jumladan PubMed bilan bog‘langan yozuvlarda, sarlavha va annotatsiya maydonlari bo‘yicha bajarildi. PubMed alohida ikkinchi baza sifatida hisoblanmadi. Birinchi so‘rov acidoCEST va yodli CEST agentlarini, ikkinchisi extracellular pH/tumor acidity/acidosis, CEST va patient/clinical/human terminlarini birlashtirdi; sana chegarasi 2016-01-01–2026-11-03 bo‘ldi. Til

bo‘yicha filtr qo‘yilmadi. Ikki so‘rovning barcha qaytgan yozuvlari olindi; DOI, DOI yo‘q bo‘lsa manba va identifikator bo‘yicha aynan takror yozuvlar chiqarildi. So‘rovlarning to‘liq matni, sonlar va tanlash sabablari elektron ilovada berildi. Hisobot oqimini ochiq bayon qilishda PRISMA 2020 tamoyillaridan foydalanildi [164].

Saralash va ma’lumot ajratishda ChatGPTdan foydalanildi; bu ikki mustaqil inson baholovchining saralashi yoki kelishuvi sifatida ko‘rsatilmadi. Protokol oldindan ro‘yxatdan o‘tkazilmagan. Hisobotlardan bemorlar soni, o‘sma turi, agent, maydon kuchi, kalibrlash diapazoni, referens, mustaqil hisob birligi, muvaffaqiyatsiz o‘lchovlar va aniqlikni baholash uchun zarur ma’lumotlar ajratildi. Bemor, o‘choq va voksel sonlari alohida saqlandi. To‘liq matn bosqichidagi chiqarish sabablari elektron ilovada qayd etildi.

QUADAS-3 v1.2 sonli diagnostik aniqlik bahosini tahlil birligi sifatida talab qiladi [165]. Shu sababli avval mos sezgirlik/spetsifiklik yoki boshqa aniqlik bahosi mavjudligi tekshirildi. Bunday baho bo‘lmagan hisobotlarga formal QUADAS-3 yakuniy xavf darajasi qo‘yilmadi; uning to‘rt domeni bo‘yicha tuzilgan metodologik audit alohida ko‘rsatildi. RoB 2 va SYRCLE tanlangan klinik kuzatuv savoliga mos bo‘lmagani uchun qo‘llanmadi. GRADEning besh domeni guruhlararo biomarker farqiga moslashtirildi [166]; bu diagnostik aniqlikning formal GRADE bahosi sifatida talqin qilinmadi.

3 pH gomeostazi va biologik muhitlar

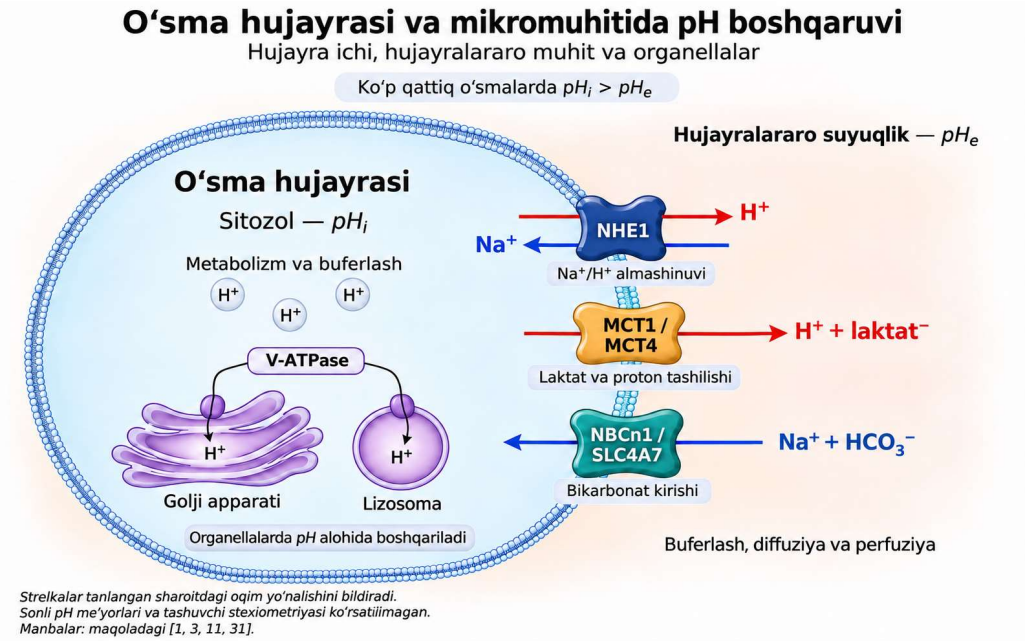
pH proton faolligining logarifmik ifodasidir va konsentratsiya birligiga ega emas. Mahalliy holatni buferlar, CO_2/HCO_3^- tizimi, metabolizm hamda membranadagi proton va bikarbonat transporti birgalikda belgilaydi. NHE1, monokarboksilat tashuvchilar va karbonat angidrazalar pHni saqlash bilan birga signal uzatish va metabolik moslashuvda ishtirok etadi [1, 2, 3]. Shu bois yagona «organ pH darajasi» ko‘pchilik biologik yoki klinik savolni yetarli ifodalamaydi.

Qon, sitozol (pH_i), hujayradan tashqari muhit (pH_e), organella va organ bo‘shlig‘i suyuqligining pHlari alohida kattaliklardir. Siydik pHini buyrak parenximasi pHiga, nafas kondensatini bronx yuzasi suyuqligiga, oshqozon bo‘shlig‘ini esa shilliq qavat hujayralariga tenglashtirib bo‘lmaydi [25, 26, 27, 28]. Biologik suyuqlik yoki ajratilgan namuna to‘qimaning bevosita ko‘rsatkichi sifatida ishlatilsa, muvofiqlik tegishli muhit va sharoitda tekshiriladi.

Gliomadagi yuqori pH_i boshqa o‘smalardagi past pH_e bilan birga mavjud bo‘lishi mumkin. Proton chiqarilishi sitozolni nisbatan ishqoriy saqlab, tashqarida proton to‘planishiga hissa qo‘shadi [1, 3, 10]. Golji apparati va lizosoma pHining o‘zgarishi esa boshqa biologik vazifani aks ettiradi [11, 29]. Davolash nishoni hujayra, muhit, vaqt va kerakli o‘zgarish miqdori bilan belgilanadi. CLC3 haqidagi ishning 5B-rasmi keyinchalik almashtirilgan; mualliflar umumiy xulosa saqlanganini bildirgan (tuzatish DOI: 10.1038/s41420-026-03008-y).

Bufer sig‘imi proton transportidan ajratib qaraladi. Bir xil proton oqimi turli buferlarda turlicha pH siljishini beradi; o‘lchangan pH kislota hosil bo‘lish tezligini bevosita ifodalamaydi. CO_2 diffuziyasi, uning HCO_3^-ga aylanishi, qon oqimi va kislorod ta’minoti mahalliy kislota yukining chiqarilishini belgilaydi. Qon ko‘rsatkichining barqarorligi to‘qima mikromuhiti ham barqaror ekanini anglatmaydi [1, 2, 3].

pHning signal uzatishdagi roli uni metabolizmning oddiy oqibati deb qarashdan kengroqdir. Gαi oqsilining tuzilishi va funksiyasini o‘rgangan ishda pHga javob beruvchi holatlar molekulyar hamda mutatsion usullar bilan aniqlangan [30]. Natija sitozoldagi proton faolligi oqsil faoliyatiga ta’sir qilishini ko‘rsatadi. Biroq ajratilgan oqsil yoki hujayra tajribasi organ darajasida diagnostik chegara belgilamaydi. Gomeostaz tahlilida ion transporti bilan birga pHga sezgir molekulyar nishonlar ham hisobga olinadi.



1-rasm. O‘sma hujayrasi va uning mikromuhitida pH muhitlari. Proton/laktat tashilishi hamda bikarbonat oqimi sitozol va tashqi muhit orasidagi gradientga hissa qo‘shadi. Organella pH gomeostazi alohida boshqariladi. Sxema muallif tomonidan [1, 3, 11, 31] asosida tuzildi; strelkalar transport yo‘nalishining soddalashtirilgan ko‘rinishi.

1-jadval. Bevosita qiyoslash chegarasini ko‘rsatadigan pH natijalari

Namuna va sharoit	O‘lchangan qiymat	Qiyosiy talqin va chegarasi
Inson gliomasi, 12 bemor; 7 T ^{31}P-MRST; pH_i [10]	Butun o‘sma 7.057 ± 0.024; normal ko‘rinadigan oq modda 7.006 ± 0.012; $p < 0.001$	Mualliflar bergan o‘rtachalar farqi 0.051. Bu oddiy ayirma, yangi effekt bahosi yoki individual diagnostik chegara emas.
Inson jigar o‘smalari; ioversol dual-power CEST; pH_e [7]	15 karsinoma: 6.66 ± 0.19; 5 gemangioma: 7.34 ± 0.09; o‘rtacha ± SD	Kichik va tarkibi turlicha guruhlar. Benign guruh o‘rtachasi maqolada ko‘rsatilgan 6.0–7.2 kalibrlash oralig‘idan yuqori.
Klinik acidoCEST pilot, ikki bemor [32]	Tuxumdon o‘smasida pH_e 6.58; ko‘krak o‘smasida kontrast yetarli emas	Bitta muvaffaqiyatli xarita referens oraliq ham, sezgirlik bahosi ham emas.
Kalamush buyragi, n = 5; iopamidol-CEST [25]	Korteks 7.0 ± 0.1; medulla 6.8 ± 0.1; kosacha 6.5 ± 0.2	Organ ichidagi gradient. Kontrast tarqaladigan sohalar inson sitozolining normal qiymatlari emas.
Sichqonda ureter to‘silishi; DCE-CEST [33]	Qarama-qarshi buyrak 6.67 ± 0.08; to‘silgan buyrak 6.79 ± 0.11	Mahalliy ajratish va perfuziya o‘zgargan sharoit. Butun organizm qonining kislotalanishi (atsidemiya) yo‘nalishini bundan xulosa qilib bo‘lmaydi.
Infeksiyalangan cho‘chqa yarasi, 13-kun [34]	Manfiy bosim: 7.23 ± 0.19; doka: 7.77 ± 0.23	Hayvon yara yuzasi natijasi. Inson diabetik yarasi uchun davolash chegarasi emas.

Izoh: ± ifodasining SD ekanligi faqat manbada tasdiqlangan joyda yozildi; qolgan qatorlarda asl hisobot shakli saqlandi. Jadval normativ atlas emas. Turli muhit va usullardagi qiymatlar bitta taqsimot sifatida birlashtirilmadi.

4 pHni o‘lchash texnologiyalari va natijalarni talqin qilish

pHga sezgirlik, mutlaq qiymatga moslik, takrorlanuvchanlik va fazoviy ajratish turli xususiyatlardir. Optik tolali sensor laboratoriyada 0.0013 pH farqini ajratgan; 22 soatdagi drift 0.003 pH, javob vaqti ikki daqiqadan qisqa bo‘lgan [5]. Tirik to‘qimada xuddi shu mutlaq aniqlikka erishish uchun kontakt, oqsil

qoplanishi, harorat va kalibrlash drifti tekshiriladi. Bioresorbsiyalanuvchi sensorning sichqonda 100 soatdan ortiq ishlashi ham insondagi uzoq muddatli implant validatsiyasiga teng emas [4].

Ekzogen acidoCEST kontrast agentning almashinuvchi protonlari orqali pH_eni baholaydi. Ratiometrik va Bloch-fitting yondashuvlari konsentratsiya ta'sirini kamaytiradi, biroq signal yetarliligi, harorat, B_0/B_1 maydonlari, perfuziya va model shartlari muhimligicha qoladi [7, 32, 35, 36]. Agent yetib bormagan vokselning xaritadan chiqishi tasodifiy yo‘qotish bo‘lmasligi mumkin: perfuziyasi past, ammo biologik ahamiyatli sohalar chetda qolishi ehtimoli tekshiriladi.

Endogen APT/amin-CEST signali pHdan tashqari oqsil miqdori va boshqa almashinish komponentlariga bog‘liq. Endogen almashinish tezligi bilan ekzogen acidoCEST pH_esi mos kelmagan ish [19] va $R_1\rho$ning makromolekula zichligiga sezgirligi [37] CEST signalini to‘g‘ridan-to‘g‘ri mutlaq pH deb talqin qilishni cheklaydi. Usullar har doim bir biologik kattalikni o‘lchamaydi.

^{31}P-MRST fosfat komponentlari to‘g‘ri ajratilganda kimyoviy siljish orqali asosan pH_ini baholaydi. Glioma ishida 5.7 mL voksel ishlatilgan [10]; bunday hajm mayda metabolik sohalarni aralashtirishi mumkin. Yurakda qondagi 2,3-difosfogliserat fosfat cho‘qqisini ajratishni qiyinlashtiradi [38]. Spektroskopiya muhim fizik referensdir, ammo barcha sharoitda xatosiz standart bo‘la olmaydi.

DeepCEST ishida 15 bemorning 11 tasi modelni o‘qitish, to‘rttasi test uchun ishlatilgan; o‘sma sohasidagi RMSE taxminan 0.04 pH bo‘lgan [8]. 3-rasmdagi fazoviy ajratish qobiliyati pasaytirilgan xaritalar qiyosida RMSE 0.036, $r = 0.45$ va $R^2 = 0.20$ berilgan. Bu ko‘rsatkichlar modelni o‘qitish va dastlabki tekshirish bosqichidagi $r = 0.71$ hamda $R^2 = 0.51$ bilan aynan bir tahlilga tegishli emas. Kichik RMSE biologik farqlarning yaxshi saqlanganini yolg‘iz o‘zi isbotlamaydi. Mayda tuzilmalarning pH bahosi pastroq fazoviy ajratish qobiliyatiga ega ^{31}P referensidan o‘rganilganligi sababli mustaqil tekshiruv talab qiladi.

Bloch-fittingni baholagan 2025 yilgi metodologik ishda 120 fantom va beshta 4T1 o‘smali sichqon o‘rganilgan; maqola annotatsiyasida natijaning to‘yintirish impulsining 3 μT B_1 amplitudasi, kamida bir soniyalik to‘yintirish, ≥15 mM iopamidol va 37.0 ± 1.5 °C sharoitlariga bog‘liqligi ko‘rsatilgan [36]. Bunday shartlar «model yaxshi ishlaydi» degan xulosaning qo‘llanish doirasini belgilaydi. Ularni boshqa zond, tana harorati yoki boshqa maydon kuchiga avtomatik ko‘chirish mumkin emas. 2026 yilgi 11 kalamushli iobitridol ishida esa PBS fantomidan olingan kalibrlash tirik to‘qimaga magnetizatsiya uzatilishi bilan bog‘liq aralashuvchi ta'sirlarni hisobga olmasdan ko‘chirilmasligi muhokama qilingan [39].

Mashinaviy o‘rganish uchun 200 fantomdan olingan 36 000 spektr foydali o‘qitish materialidir, ammo 36 000 mustaqil biologik namuna emas [40]. Fantom, hayvon va inson ma'lumotlarida harorat, oqsil, perfuziya va harakat farq qiladi. Shuning uchun fantomdagi regressiya xatosi, sichqondagi model-referens mosligi va bemordagi klinik diskriminatsiya alohida baholanishi lozim [8, 35, 40]. Shovqinni kamaytirish algoritmlari signal sifatini yaxshilashi mumkin [41]; shu bilan birga haqiqiy kichik kislotali sohalarning silliqlash jarayonida yo‘qolishi mumkinligi mustaqil referens bilan tekshirilishi kerak. Bu ehtimol metodologik savol bo‘lib, algoritm bunday xatoga yo‘l qo‘ygani haqidagi tasdiqlangan natija emas.

Nanoskopik CEST polimeri, monomer zond va iopamidol bergan turli pH baholari zond tuzilishi signal kuchi bilan birga kalibrlashga ham ta'sir qilishini ko‘rsatadi [42]. Ferment faolligi va pHni bitta agentda kuzatish foydali, biroq ularning signalga qo‘shgan hissasini ajratish talab etiladi [43, 44]. Boshqa tamoyilga asoslangan mustaqil o‘lchov, masalan, ferment faolligini LC–MS orqali baholash, talqinni mustahkamlaydi [43].

Agentni yuborish yo‘li o‘lchov qamrovini belgilaydi. Ortoptik pankreatik o‘sma modelida intraperitoneal iopamidol vena ichiga yuborilgan agentdan kechroq yetib borgan; pH baholari qiyosida $p = 0.16$ olingan [45]. Statistik farq topilmagani oldindan belgilangan ekvivalentlik chegarasisiz usullar tengligini isbotlamaydi. Ko‘p kesimli CEST o‘sma markazi, cheti va buyrak gradientlarini kengroq qamragan [46], lekin har bir vokselda yetarli agent va to‘g‘ri kalibrlash baribir zarur.

Optik yondashuvlarga fluoressensiya davomiyligiga asoslangan SypHerRed, membranaga bog‘langan pHLuc va ratiometrik xemilyuminessent zondlar kiradi [47, 48, 49]. Genetik raporter hujayra yoki uning sirtini modelda kuzatadi; u bemorga yuborishga tayyor diagnostik agent bilan teng emas. Ferment

bilan faollashuvchi DNA nanosensori ishemik shikastlanishni ajratishga qaratilgan [50], ammo signalga zond yetib borishi va ferment miqdori ham ta'sir qiladi. Fotoakustik/NIR-II zond [51] va EPR profillash [52] chuqurlik va mikromuhit axborotini kengaytiradi; mavjud korpus ular uchun insondagi universal aniqlik bahosini bermaydi.

Giperpolyarizatsiyalangan tasvirlashda yuborilgan prekursor muhimdir. Bikarbonatning hujayradan tashqari taqsimlanishi piruvatdan hujayra ichida hosil bo'ladigan HCO_3^-/CO_2 signalidan farq qiladi [53, 54, 55]. Alanin etil esterining transporti va metabolizmiga asoslangan usul ikkala muhitni ajratishga intilgan [56]. Impuls ketma-ketligida ikki yo'nalishli almashinishni hisobga olish signalni yaxshilaydi [57], ammo muvozanatga yetmagan nisbatning pH talqini cheklangan. Klinik tatbiqqa mos ^{13}C-bikarbonat ishi hayvonlarda klinik 3 T skanerda bajarilgan [58]; bu bemorda validatsiya o'tkazilganini anglatmaydi.

2-jadval. O'lchash texnologiyalarining analitik xususiyatlari va klinik tatbiqi

Usul va fizik tamoyil	Kuchli jihati; tekshirilgan misol	Asosiy cheklov va validatsiya ehtiyoji
Elektrokimyoviy elektrod: potensialning proton faolligiga javobi	Kontakt joyda uzluksiz o'lchash; chuqur to'qima uchun miniaturizatsiya [6]	Chuqur kiritish invaziv; signal siljishi (drift) va sensor sirtining biologik qatlam bilan qoplanishi. Ter yoki yara sensori chuqur organ xaritasi emas [59].
Optik intensivlik, nisbat yoki fluoressensiya davomiyligi	Mahalliy yoki hujayraviy kuzatuv; optik tolada laboratoriyada 0.0013 pH farqini ajratish [4, 5, 47]	Sochilish, fotobarqarorlik, zondning joylashuvi; chuqur organlarga kirish cheklangan.
^{31}P-MRS/MRST: fosfat kimyoviy siljishi	Endogen metabolik referens; inson gliomasi va yurakda qo'llangan [10, 38]	Past signal, qisman hajm effekti, Pi cho'qqilari aralashishi; gliomada 5.7 mL voksel.
Ekzogen CEST, jumladan acidoCEST: almashinish va ratiometrik/model tahlili	pH_e xaritasi; inson jigar o'smasi va klinik pilot [7, 32]	Kontrast yetib borishi, konsentratsiya, maydon va haroratga bog'liqlik; protokolga xos kalibrlash.
Endogen CEST yoki $R_1\rho$: almashinishga sezgir signal	Kontrast yubormasdan metabolik muhitni kuzatish [60, 61, 62]	pH va makromolekula miqdorini ajratish qiyin; mutlaq pHga tenglashtirilmaydi [19, 37].
Giperpolyarizatsiya ^{13}C: HCO_3^-/CO_2 nisbati yoki zond siljishi	Tez metabolik tasvirlash; Z-OMPD $T_1 \approx 2$ min, 1 T; 1.9 ppm/pH gacha [9, 55]	Qisqa signal oynasi, kimyoviy muvozanat va muhit, ishlab chiqarish hamda xavfsizlik [58, 63].
PET, EPR va fotoakustik zondlar	Chuqur signal yoki mikromuhit profili; 2024–2026 preklinik ishlar [51, 52, 64]	Signal zond kinetikasiga ham bog'liq; klinik mutlaq pH aniqligi uchun alohida dalil kerak.
Mashinaviy o'rganish bilan CEST tahlili	38 sichqonli ishda test MAE 0.054 pH; inson DeepCEST testi n = 4 [8, 35]	Referensdagi xato modelga o'tadi; ko'p voksel mustaqil ko'p bemor emas. Tashqi markaz testi zarur.

Izoh: bitta universal «aniqlik» yoki fazoviy ajratish raqami berilmadi, chunki maydon kuchi, zond, protokol va biologik namuna turlicha. ppm/pH signal sezgirligi bo'lib, pH xatoligining o'zi emas. Qon yoki bo'shliq pH darajasi monitoringi bilan chuqur to'qima tasvirlashining invazivligi ham bir xil emas.

5 Organlar va kasalliklar bo'yicha qiyosiy sintez

5.1 Buyrakda kislota chiqarilishi va mahalliy pH

Qon bikarbonati, siydik pHi, ammoniy chiqarilishi va parenxima pHi buyrak faoliyatining turli tomonlarini ko'rsatadi. Siydik pHi sof kislota chiqarilishini to'liq tavsiflamaydi va ammoniy bilan birga talqin qilinadi [26]. Distal renal tubulyar atsidoz registrlari va RhBG ishlari genetik nuqsonni klinik fenotip bilan bog'laydi [65, 66, 67], biroq tasvirdagi har bir mahalliy pH o'zgarishining mexanizmini tasdiqlamaydi.

Ureter to'silganda CEST pHining yuqoriroq bo'lishi [33] surunkali buyrak kasalligida qon bikarbonati pasayishiga zid emas. Birinchisi kontrast ajralishi, perfuziya va mahalliy siydik muhitiga,

ikkinchisi tizimli kislota-asos balansiga tegishli. Ishemiya–reperfuziya modellarida ham pH va perfuziyani birga kuzatish kerak [68, 69]. Buyrak CESTini eGFR o‘rniga qo‘llashdan avval signal qaysi fiziologik komponentni ifodalashi aniqlanadi.

Yangi funksional-genetik dalillar natijani tushuntirish imkonini kengaytiradi. RhBG ishida CRIC ma’lumotlaridan 507 Afrika va 1147 Yevropa ajdodli ishtirokchining ekzom (gen oqsil kodlovchi qismlari) ma’lumotlari tekshirilgan [67]. Noyob variantning kasallik bilan statistik bog‘liqligi uning NH_3/NH_4^+ tashilishini o‘zgartirishi haqidagi funksional tajribadan farqli dalildir. Mualliflar kam uchraydigan variantlar soni va jins bo‘yicha guruhlarga ajratishdagi cheklovni qayd etgan. Shu bois bitta tashuvchi genidan barcha bemorlardagi siydik pH darajasi yoki atsidoz og‘irligini chiqarish asosli emas.

Klinik natijalar ham aralashuvning erishilgan darajasiga bog‘liq. Bikarbonatning hayot sifatiga uzoq muddatli ta’sirini baholagan pragmatik sinov annotatsiyasida aniq yaxshilanish kuzatilmagani va maqsad darajaga erishish cheklangani bildirilgan [70]. Bu xulosa BiCARB va VALOR-CKD bilan yo‘nalish jihatidan mos keladi, lekin dizayn, populyatsiya va yakunlar bir xil bo‘lmagani sababli ularning sonlari ushbu sharhda birlashtirilmadi [23, 24].

5.2 Oshqozon va qizilo‘ngachda pH monitoringi

Qizilo‘ngach pH va impedans (elektr qarshiligi) monitoringi uchun klinik mezonlar boshqa ko‘plab to‘qima pH texnologiyalariga qaraganda yaxshiroq shakllangan; Lyon 2.0 konsensusi bunday talqinning tayanchidir [71]. Shunga qaramay, datchik joylashuvi, yozuv davomiyligi va kunlararo o‘zgarish diagnostik tasnifga ta’sir qiladi [72, 73, 74]. 944 tekshiruvli ishda 24, 48 va 72 soatlik manba sezgirligi mos ravishda 62.5%, 76.6% va 88.2% bo‘lgan, ammo referens o‘sha manbaning 96 soatlik natijasidir [75]. Bu tashqi mustaqil diagnostik standartga nisbatan aniqlik emas.

pHoenix Score 318 bemorda chegaraviy natijalar ulushini 11% dan 4.7% ga kamaytirgan [76]. Yangi indeks va DeMeester referensi bir pH yozuviga tayansa, moslikning bir qismi umumiy ma’lumotdan kelishi mumkin. Milan Score uchun AUC 0.812 manometriya indeksining pH orqali belgilangan gastroezofageal reflyuks kasalligini ajratishini bildiradi, sensor aniqligini emas [77]. Raqamni baholashda indeks test va referens birga ko‘rsatiladi.

Oshqozon bo‘shlig‘i pHini dori bilan boshqarish mahalliy farmakodinamikaning amaliy misolidir. Besh sog‘lom ko‘ngillidagi besh davrli krossover pilot proton nasosi ingibitorlarini qiyoslagan [27]. Takroriy davrlar shaxslararo farqni kamaytiradi, ammo besh kishini katta mustaqil tanlanmaga aylantirmaydi. Intragastrik pH tafovuti simptom yengillashishi, eroziya bitishi yoki uzoq muddatli ustunlikni bevosita tasdiqlamaydi.

So‘lak va og‘iz biofilmining 96 soatlik pilotiga 12 ishtirokchi kiritilib, 11 nafari yakunlagan [78]. Ovqat, glyukoza va mahalliy biofilm bir og‘iz bo‘shlig‘ida ham turli pH trayektoriyalarini yuzaga keltiradi. Funksional jig‘ildon qaynashini 24 soatlik MII-pH asosida qayta tasniflash [79] vaqt oynasi va klinik kuzatuv ahamiyatini ko‘rsatadi. Kattalardagi mukovissidozda distal yo‘g‘on ichak pHi ilgari yig‘ilgan kapsula ma’lumotlaridan qayta tahlil qilingan [80]; bu yangi mustaqil kohorta emas.

5.3 Miya kasalliklarida pH o‘zgarishlari

Ishemik insultda atsidoz va oksidlovchi stressning vaqt bo‘yicha kechishi farq qiladi. Kemiruvchilardagi dinamik kuzatuv kislotalilikni bitta statik yakun bilan ifodalash yetarli emasligini ko‘rsatgan [81]. ASIC1a bilan bog‘liq shikastlanish [82] va ayrim Parkinson hujayra modellarida metabolik kislotalanishning mitofagiya orqali himoyasi [83] boshqa kasallik, vaqt va jarayonlarga tegishli. Ular bemor miyasini umumiy kislotalashtirish uchun asos bo‘lmaydi.

APT yoki ratiometrik CEST insult bilan bog‘liq o‘zgarishlarga sezgir bo‘lishi mumkin [62, 84], lekin CEST usullarining o‘zaro korrelyatsiyasi mustaqil mutlaq pH validatsiyasi emas. Bosh miya jarohati haqidagi ^{31}P-MRS ishining tuzatilgan hisobotida strukturaviy MRT o‘zgarishlari kam bo‘lgan sohalarda ham metabolik farqlar qayd etilgan [85]. Uning tuzatish nashrida (corrigendum) pH medianalari, ayrim p-qiymatlar va jadvallar tuzatilgan (DOI: 10.1177/0271678X19853211). Shu sababli dastlabki nusxadagi miqdoriy natijalar tuzatilgan matn bilan solishtirilishi kerak. Usulning prognozga qo‘shimcha qiymati mustaqil klinik kohortada tekshirilishi lozim.

Parkinson kasalligining 7 T ^{31}P-MRS ishida 19 bemor va 19 nazorat ishtirokchisi ikki metabolik o‘lchov kohortasiga bo‘lingan [86]. Metabolit nisbatining o‘zgarmasligi mutlaq miqdor yoki oqim saqlanganini bildirmaydi. Oksipital sohadagi natijani substantia nigra holatiga tenglashtirish ham to‘g‘ri emas. Serebrovaskulyar boshqaruv sharhi arterial va perivaskulyar pHni ajratish hamda CO_2 diffuziyasini hisobga olishni asoslaydi [87].

Gliomada 2025 yilgi 11 bemorli ^{31}P siljish tahlili avvalgi, jumladan 12 bemorli 2024 yilgi ish ma’lumotlaridan qayta foydalangan [10, 88]. Bu mustaqil replikatsiya emas. ATP siljishlariga Mg^{2+} ham ta’sir qilishi va sog‘lom nazorat guruhi yosh bo‘yicha to‘liq mos kelmagani pHdan tashqari chalkashtiruvchi omillardir [88]. Fosfat spektridagi farqni faqat proton faolligiga nisbatlash o‘sma mikromuhitining boshqa ion xususiyatlarini yo‘qotishi mumkin.

5.4 Yurak va mushaklarda pH va metabolik jarayonlar

12 sog‘lom ishtirokchi va uch HCM bemorini qamragan 7 T ^{31}P-MRS dasturida ayrim ishtirokchilar bir nechta tajribada qatnashgan. HCM qiyosida energetik nisbatlar o‘zgargan, pH_i farqi esa aniqlanmagan ($p = 0.508$) [38]. Uch bemorli pilotdagi neytral natija kasallik mavjudligini inkor etmaydi va usulning diagnostik sezgirligi pastligini qat’iy isbotlamaydi. Shu ishda pH takrorlanuvchanlik koeffitsiyenti 0.052 bo‘lgan. Boshqa organdagi kichik o‘rtacha pH farqini shu raqam bilan bevosita diagnostik chegara sifatida qiyoslash mumkin emas.

Reperfuziya boshida kislotalilikni saqlash ayrim hayvon modellarida himoya bergan [89, 90]. Giperglikemiyada kardiomiotsit NHE1ining ortiqcha ifodalanishi ham himoya bilan bog‘langan [91]. Boshqa tomondan, SLC4A3ga aloqador iPSCdan olingan inson kardiomiotsitlarida ishqoriylashish aritmogen mexanizmda ishtirok etgan [92]. Natija transport oqimi, Na^+/Ca^{2+} balansi, kasallik bosqichi va muhitga bog‘liq. Karnozin hamda β-alanin dalillari yuklamadagi skelet mushagi buferlanishiga tegishli; ular tinch yurak pHiga ko‘chirilmaydi [93].

Yurak miotsitlarida kislota chiqaruvchi va yuklovchi tashuvchilarning o‘zaro nisbati pHni belgilaydi [94]. Gipoksiyada NHE1 faolligining susayishi [95] tashuvchi faolligi faqat ifodalanish miqdori bilan aniqlanmasligini ko‘rsatadi. NBCn1 yo‘qotilgan sichqonda bo‘lmachadagi kislota chiqarilishi susaygan, arterial bosim va gipertrofiya oshgan [96]. Butun organizmda genni o‘chirish (global nokaut) holatida to‘g‘ridan-to‘g‘ri yurak ta’siri bilan gipertenziya orqali bilvosita ta’sirni to‘liq ajratish qiyin. Sitozol va tashqi muhit atsidozining metabolomga turlicha ta’siriga oid jurnal ishi annotatsiyasi [97] ushbu muhit farqiga mos keladi; topilgan 2022 yilgi preprint jurnalning yakuniy to‘liq matni sifatida hisoblanmadi.

5.5 Nafas yo‘llari va mukovissidozda pH o‘zgarishlari

Yangi tug‘ilgan mukovissidozli cho‘chqalarda ASL pHining pastligi bakteriyalarni yo‘qotishni susaytirgan [98]. Bolalardagi in vivo o‘lchov kislotalanishni tasdiqlamagan [99]; boshqa cho‘chqa ishida ham farq topilmagan [100]. Demak, tafovut faqat tur farqi bilan izohlanmaydi. Anatomik soha, yosh, yallig‘lanish, paratsellyular HCO_3^- oqimi, hujayra tarkibi va o‘lchov sharoiti ehtimoliy omillardir [20, 101, 102, 103].

Dinamik tadqiqot 10 nazorat va 11 mukovissidoz ishtirokchisida nafasga bog‘liq nazal pH tebranishlarini o‘rgangan [104]. Qisqa ishqoriy cho‘qqilar doimiy o‘pka normasini belgilamaydi. CFTR modulyatorlari shilliq xossalarini pH tiklanishidan ko‘ra gidratatsiya orqali yaxshilagani [105] foydani faqat pH bilan tushuntirishni cheklaydi. Nazal, bronxial va nafas kondensati o‘lchovlari alohida talqin qilinadi [28, 101].

Mexanistik tajribada pH va HCO_3^- ta’sirlari ajratiladi. Yangi tug‘ilgan cho‘chqa ASLida pH va HCO_3^-/CO_2ni turlicha o‘zgartirish kislotalanishning shilliq qovushqoqligiga ta’sirini qo‘llab-quvvatlagan [106]. Ajratilgan shilliq diffuziyasi mukotsiliar transportning butun mexanikasini qamramaydi. Ivakaftorda guruhning o‘rtacha ASL pHi sezilarli o‘zgarmagan, individual siljishlar esa ter xloridi pasayishi bilan korrelyatsiyalangan [107]. Guruh o‘rtachasi va individual o‘zgarishlar korrelyatsiyasi boshqa statistik savollarga javob beradi.

SERS mikrosensorlari olti mukovissidozli va olti mukovissidozsiz donorning havo–suyuqlik interfeysi kulturalarida tekshirilgan; ayrim tajribalarda kichikroq donor guruhlari ishlatilgan [108]. Nazal

hujayralardagi TMEM16A va SLC26A4 ishida uch donorning takroriy o‘lchovlari mavjud [109]. Nazal va bronxial oqsillarni qiyoslagan 2026 yilgi ishga muvaffaqiyatli o‘stirilgan uch nafardan donor kirgan [101]. Texnik takror, hujayra va donor sonlari shu sababli alohida beriladi; ko‘p o‘lchov mustaqil donorlar sonini oshirmaydi.

WNK ingibitsiyasi bilan ASL pH darajasi va himoya funksiyasining yaxshilanishi insondan olingan kulturalarda ko‘rsatilgan [110]; buni bemordagi infeksiya yoki o‘pka funksiyasi foydasi sifatida talqin qilish erta. Nafas kondensati elektrodini baholagan ishda inson namunalari ikki sog‘lom ko‘ngillidan takroriy kunlarda yig‘ilgan [28]. Bunday sensor tadqiqoti populyatsion normal pHni belgilamaydi. Astma bilan bog‘liq AUC 0.72 natijasi [111] esa namuna olish sharoiti, harorat, namlik va ifloslantiruvchilar bilan bog‘liqlik [112] hisobga olinganda baholanishi kerak.

5.6 Jigar va yara sohasida pH o‘zgarishlari

Jigar yulduzsimon hujayralarida perisinusoidal kislotalilik safro tuzlari ta’sirini kuchaytirishi, NHE1 va V-ATPase jarayonlari esa fibrogen holat bilan bog‘liqligi ko‘rsatilgan [113, 114, 115]. Hujayra tajribasi va DDC sichqon modelidagi pantoprazol natijasi inson fibrozining standart davosini isbotlamaydi [113]. Jigar saratonining past pH_esi ham barcha klinik vaziyatlar uchun tayyor diagnostik chegara emas [7].

Diabetik oyoq yarasi bo‘yicha prospektiv ishda 235 dastlabki ishtirokchidan 187 nafari yakuniy tahlilga kirgan va 1531 o‘lchov nuqtasi qayd etilgan [116]. 1531 soni mustaqil bemorlar sonini bildirmaydi. 142 bemor kuzatuvi to‘liq yakunlanmagan (senzuralangan); 136 holatda buning sababi noma’lum deb ko‘rsatilgan. Yara tubi pH darajasi <6.7 bo‘lganda uch kun ichida bitishni ajratish sezgirligi 75.7%, spetsifikligi 72.7%; yara cheti pH darajasi <6.8 bo‘lganda esa 88.0% va 75.8% bo‘lgan. Takroriy o‘lchovlar bog‘liqligi, chegaraning ayni kohortada tanlanishi va ko‘p kuzatuvlarning senzuralanishi tashqi validatsiyasiz umumlashtirishni cheklaydi. Hujayralar ko‘payish (proliferativ) bosqichiga o‘tishni bashorat qiluvchi yuqori pH chegarasi boshqa yakunga tegishli bo‘lib, ushbu bitish natijasiga bevosita zid emas.

Jigardagi Na^+/H^+ almashinuvi sharhi gepatotsit, xolangiotsit va yulduzsimon hujayralarning vazifalarini ajratadi [117]. Safro bo‘shlig‘i, sitozol va perisinusoidal mikromuhit natijalari yagona jigar pHiga birlashtirilmaydi. Deep Image Prior bilan tasvirni yaxshilash 49 quyonda o‘rganilgan, lekin yuqori ajratishdagi referens faqat ikki hayvonda olingan [118]. Katta umumiy tanlanma kichik referens to‘plami cheklovini yo‘qotmaydi.

Bo‘g‘im to‘qimalarida 3 T acidoCEST-UTE texnologiyasi qisqa T_2li tog‘ay va meniskka moslashishga intilgan [119]. Osteoartritda kislotalilikning simptomlar bilan bog‘lanishi [120] yallig‘lanish, perfuziya va degeneratsiya ta’siridan ajratilishi kerak. Ushbu osteoartrit maqolasining pH rang shkalasiga tuzatish e’lon qilingan; yakuniy talqinda tuzatilgan 6.5–8 diapazon inobatga olindi (tuzatish DOI: 10.3390/ijms241512346).

Yara bitishi uchun pastroq pH bilan ijobiy bog‘liqlik mavjud bo‘lsa-da, muayyan aralashuvning samarasi alohida tekshiriladi. Trigona asali qo‘llangan to‘rt DOY holatida ikki yara bitgan, ikkitasi sakkiz haftada bitmagan [121]. Nazorat guruhining yo‘qligi, yara og‘irligi va birga olib borilgan parvarish ushbu natijani asal yoki faqat pH ta’siriga nisbatlashni cheklaydi. Cho‘chqada manfiy bosimli yara terapiyasi (NPWT) ishida yara pH darajasi bilan bakterial yuk birga o‘zgargan [34], ammo perfuziya va mexanik ta’sir ham mavjud; pH sababiy vositachi ekanini alohida vositachilik tahlilisiz tasdiqlab bo‘lmaydi.

3-jadval. Organlarga xos dalil va xulosa chegarasi

Organ yoki namuna	**Tayanch dalil**	**Asoslangan talqin; hali isbotlanmagan jihat**
Buyrak	Siydik pH darajasi va ammoniy; lokal CEST; klinik RCTlar [23, 26, 33]	Kislota chiqarilishi, mahalliy pH va kasallik rivojlanishi alohida yakunlar. Bir biomarker ikkinchisini to‘liq almashtirmaydi.
Qizilo‘ngach/oshqozon bo‘shlig‘i	Ambulator monitoring va konsensus [27, 71, 75, 76]	Klinik diagnostika uchun qo‘llanish mavjud; davomiylik va referens tanlovi aniqlikka ta’sir qiladi.

Organ yoki namuna	Tayanch dalil	Asoslangan talqin; hali isbotlanmagan jihat
Miya	Insult dinamikasi va CEST/MRS [62, 81, 84, 85]	Metabolik axborot mavjud; signalning barcha o‘zgarishini mutlaq pHga nisbatlash mumkin emas.
Yurak/mushak	HCMda pH neytral, energetika buzilgan; reperfuziya modellarida vaqt omili [38, 89, 90, 93]	pH universal kasallik markeri emas. Vaqtinchalik atsidoz ta’siri surunkali atsidoz bilan teng emas.
Nafas yo‘li yuzasi	Mukovissidozga zid statik natijalar, dinamik tebranishlar [98, 99, 100, 104]	Mikrosoha va vaqt bo‘yicha standartlashtirish zarur; Mukovissidozning barcha yoshida bir xil atsidoz isbotlanmagan.
Jigar	Yulduzsimon hujayralar (HSC) mexanizmlari, inson o‘smasi CEST piloti [7, 113, 115]	Fibroz (to‘qimaning chandiqlanishi) mexanizmi va saratonni aniqlovchi diagnostik tasniflagich alohida dalil talab qiladi.
Yara sohasi	Prospektiv DOY kuzatuvi va cho‘chqa aralashuvi [34, 116]	pH jarayonni kuzatishi mumkin; kuzatuvdan sababiy terapevtik maqsad chiqarilmaydi.

6 O‘sma mikromuhitida pH boshqaruvi va biologik oqibatlar

Aerob glikoliz, proton chiqarilishi, CO_2 gidratatsiyasi, perfuziya va buferlash o‘sma pH_esini birgalikda shakllantiradi [1, 3]. Ayrim modellardagi kuchli laktat–pH korrelyatsiyasi [21] barcha o‘smalarda bir xil kislota manbai yoki sababiy yo‘l borligini bildirmaydi. 2025 yilgi CRISPR ishi atsidozga javoban ERK signali va mitoxondrial nafas moslashuvini ko‘rsatgan [122]. Kislotali o‘sma shu bois faqat glikolizga qaram hujayralardan iborat deb qaralmaydi.

Kislotalilik oziqa olish, membrana xossalari va immun nazoratga ham ta’sir qiladi. Bunga ko‘krak va pankreatik saraton hujayralarida yog‘ kislotalari yutilishi [123], glioblastoma glikokaliksining qayta tuzilishi [124] va kolorektal jigar metastazlarida rezident NK hujayralarning shikastlanishi misol bo‘ladi [125]. Hujayra yoki sichqonda aniqlangan mexanizm bemordagi invaziya, metastaz va davolash javobining mustaqil prognostik belgisi ekanini avtomatik tasdiqlamaydi.

Ferroptoz ishlari muhitning ahamiyatini ko‘rsatadi. Hujayradan tashqari atsidozni kamaytirish immun javobga yordam berishi, Golji yoki boshqa organella pHini buzish esa saraton hujayrasining yashovchanligini pasaytirishi mumkin [11, 31, 126]. TMEM87A ishida Golji gomeostazi ferroptozga sezgirlik bilan bog‘langan [11]. Bu turli nishonlardir; ularni kislotalilikning mutlaq zarari yoki ishqoriylikning mutlaq foydasiga keltirib bo‘lmaydi.

O‘sma atsidozini qayta aloqa jarayonining bir qismi sifatida tushunish dalillarga mos keladi. Sharhlar pH transportini Warburg fenotipi bilan bog‘laydi [1, 3, 127]; matematik modellar CO_2/HCO_3^-, kislorod va metabolik oqimlarning turli kombinatsiyalari o‘xshash pH berishini ko‘rsatadi [128]. Modeldagi 6.7–7.4 diapazon insonda o‘lchangan referens emas. Parametrlar ham mustaqil tajriba bilan tekshiriladi.

Miyelomali sichqon suyak iligida pH_e va GLUT1ning teskari bog‘liqligi atsidozning metabolik fenotip bilan aloqasini ko‘rsatgan [129]. 4T1 va 67NR qiyosida kislotali sohalar geterogenligi agressivlik bilan birga kuzatilgan [130]. Bir hayvondagi ikki o‘sma ikki mustaqil hayvon sifatida sanalmaydi. Kolorektal saratondagi disadgerin–CA9 bo‘yicha genetik va funksional natijalar kislotalilikka moslashuvni tushuntiradi [131]; ekspressiya assotsiatsiyasi, nokaut ta’siri va bemordagi foyda esa alohida dalil darajalaridir.

T hujayralaridagi funksional pasayish, regulyator T hujayralar moslashuvi va mieloid komponent bir xil pH muhitiga turlicha javob beradi [132, 133]. Shu sababli immun hujayralarga ta’sirni faqat umumiy o‘sma pH darajasiga qarab bashoratlash cheklangan. Muhitga yo‘naltirilgan yondashuvlar haqidagi sharh [134] pHni o‘zgartirish nishonga yetib borish, hujayra o‘limi va immun faollik bilan birgalikda kuzatilishi kerakligini ta’kidlaydi. Bu nazariy mezonlar yangi ferroptoz va immunoterapiya platformalarini qiyoslash uchun foydalidir.

4-jadval. Saraton mexanizmlari bo‘yicha dalillarning o‘zaro bog‘lanishi

Yo‘nalish va model	Asosiy topilma	Qiyosiy ahamiyati
Glioma, inson ^{31}P-MRST [10]	pH_i yuqoriroq; Ki-67 bilan $r_s = 0.78$, $p = 0.001$	Proliferatsiya bilan bog‘liqlik; sababiyat yoki mustaqil diagnostik aniqlik emas.
Ko‘krak/pankreatik hujayralar [123]	Atsidozda lipid yutilishi tezlashgan	Past pH oziqa almashinuvini ham o‘zgartiradi; glikolizdan tashqari moslashuv.
Glioblastoma, eksperimental ish [124]	Glikokaliks qayta tuzilishi, lipid olish va ferroptozga ta’sir	Bir xil pH sharoiti hujayra yuzasi tarkibiga ko‘ra boshqa natija berishi mumkin.
Kolorektal jigar metastazi, inson materiali va eksperiment [125]	Kislotalanish NK hujayralarning dasturlangan o‘limi (apoptoz) bilan bog‘langan	Immunitetni susaytiruvchi mexanizm; klinik pH-neytrallash foydasini alohida sinash kerak.
TMEM87A, hujayra va sichqon [11]	Golji pH darajasini saqlash ferroptoz rezistentligiga hissa qo‘shgan	Organella pH darajasi bilan tashqi pHni ajratish zarur.
SLC4A7, NSCLC modellari [31]	Ichki kislotalanish va tashqi ishqoriylashish immun javob bilan bog‘langan	Ikki muhitli strategiya; klinik samaradorlik hali ko‘rsatilmagan.
Syrosingopin, hujayra va sichqon [135]	Hujayraviy ta’sir in vivo pH_e yoki birlamchi o‘sma o‘sishida sezilarli farqqa ko‘chmagan	Nishonni ingibitsiya qilish doimo mikromuhit va o‘sma yakunini o‘zgartirmaydi.

7 pH asosida saraton diagnostikasining klinik dalillari

Insondagi ekzogen CEST o‘sma kislotaliligini o‘lchash imkonini ko‘rsatgan [7, 32]. Jigarda 6.66 va 7.34 o‘rtachalari ajralgan bo‘lsa-da, maqoladagi kalibrlash diapazoni 6.0–7.2 edi [7]. Yaxshi sifatli guruh bahosi undan yuqori. Bu ekstrapolyatsiya va o‘lchov ishonchliligi haqidagi ochiq masaladir; natijani bekor qilmaydi. Kichik pilotdan tayyor klinik tasniflagich, ikki o‘rtachadan esa diagnostik chegara yoki AUC hosil qilinmadi.

ONM-100ning 30 bemorli dastlabki ishida to‘qqiz musbat jarrohlik chekkasining barchasi topilgan [18]. Chekka spetsifikligi ko‘krak saratonida 75%, HNSCCda 57% bo‘lgani sababli bu umumiy 100% aniqlik emas. AUC 0.9875 doza kengaytirish guruhidagi 15 bemorning 59 kesimiga tegishli. Keyingi 13 bemorli HNSCC hisoboti ayni NTR7085/EudraCT 2017-003543-38 dasturining qayta tahlili ekani to‘liq matndan tasdiqlangan [136]; bemorlar soni qo‘shilmadi.

O‘pka o‘smalarining dastlabki fluoressensiya natijasi [16] keyingi 20 bemorli II fazadagi 31.6% sezgirlik va 33.3% spetsifiklik bilan birga talqin qilinadi [15]. Biologik g‘oya saqlansa-da, mazkur protokol yetarli diagnostik natija bermagan. Peritoneal metastaz ishida 40 baholanadigan bemorning 20 tasida qoldiq kasallik topilgan [17]. Bu 50% qo‘shimcha aniqlash ulushi bo‘lib, diagnostik sezgirlikni bildirmaydi.

pHga asoslangan ajratishning preklinik misollari saraton va yallig‘lanishni to‘liq ajratadigan universal marker mavjudligini ko‘rsatmaydi. O‘pka ishida yettita erkak sichqondagi adenokarsinoma beshta urg‘ochi sichqondagi zamburug‘li granuloma bilan qiyoslangan; yosh, kasallik rivojlanish vaqti va modelning o‘zi farqlangan [137]. Shunday dizaynda pHning malignlikka xos ta’siri bilan guruhlar tarkibi ta’sirini to‘liq ajratish qiyin. Ko‘krak va jigar modellaridagi ioversol xaritalari [138] ham inson diagnostik aniqligi uchun bevosita dalil emas.

Pankreatik saraton–pankreatit modeli pH_e shakllangan saratonni yallig‘lanishdan ajratishini, ammo keyin saratonga o‘tadigan pankreatitni o‘z-o‘zidan so‘nadigan holatdan oldindan farqlamasligini ko‘rsatgan [139]. Differensial tashxis va kelajak xavfi boshqa vazifalardir. FDG-PET va CEST birlashmasi glyukoza yutilishi va atsidoz haqida axborot beradi [140]; pHga sezgir PET substratlari ham imkoniyat yaratadi [64]. Oddiy FDG yutilishi pH o‘lchovi emas, faollashuvchi zond to‘planishi esa farmakokinetikaga ham bog‘liq.

Giperpolyarizatsiyalangan prostata modelida minimum voksel pH_esi va maksimal laktat/piruvat nisbati o‘rtasidagi korrelyatsiya kuchli bo‘lgan, o‘sma bo‘yicha o‘rtachalar korrelyatsiyasi esa statistik ahamiyatga yetmagan [141]. Belgining minimumi, maksimumi va o‘rtachasi turli biologik xususiyatlarni

ajratadi; natijani qulay ko‘ringan statistik birlikka qarab tanlash xolislikni buzishi mumkin. Shu bois kelgusi klinik protokolda qaysi fazoviy ko‘rsatkich asosiy biomarker ekani oldindan belgilanishi zarur.

5-jadval. Klinik diagnostik tadqiqotlar va hisob birliklari

Tadqiqot va dizayn	Miqdoriy natija	Klinik validatsiya chegarasi
AcidoCEST, ikki bemorli translatsion pilot [32]	Bir o‘sma pH_esi 6.58; ikkinchisida yetarli kontrast yo‘q	Bajarish mumkinligi; sezgirlik/spetsifiklik aniqlanmagan.
Jigar o‘smasi CEST, 15 + 5 bemor [7]	Karsinoma 6.66 ± 0.19; gemangioma 7.34 ± 0.09	B_1, harakat, past SNR va kalibrlashdan tashqari yuqori qiymat.
Glioma ^{31}P-MRST, n = 12 [10]	pH_i va Ki-67: r_s = 0.78; p = 0.001	Korrelyatsiya; tashqi klassifikator testi yoki AUC emas.
DeepCEST, n = 15; test n = 4 [8]	O‘sma ROI RMSE ≈0.04 pH	Model-referens mosligi; mustaqil klinik natija validatsiyasi emas.
ONM-100, I faza, n = 30 [18]	Musbat chekka 9/9; AUC 0.9875 – 15 bemorning 59 kesimi	Kichik tanlanma va kesimlar ichki bog‘liqligi; bemor darajasida tashqi validatsiya kerak.
HNSCC qayta tahlili, n = 13 [136]	Musbat chekka 6/6; TBR >1.5 mezoni	[18] bilan bir dastur; mustaqil takroriy tasdiq emas.
Pegsitacianine, o‘pka II faza, n = 20 [15]	19 malign o‘choqdan 6 tasi yorqin: 31.6%; 3 benign o‘choqda spetsifiklik 33.3%; PPV 75%; NPV 7.1%	Benign o‘choqlar soni juda kam. Bemor va o‘choq birliklari aralashtirilmaydi.
Pegsitacianine, peritoneal II faza [17]	50 kiritilgan, 40 baholangan; 20/40 qoldiq kasallik	Nazoratsiz qo‘shimcha aniqlash; qaytalanish yoki yashovchanlik foydasi ko‘rsatilmagan.

Diagnostik validatsiya o‘lchovning ishonchliligi, kasallikni ajratish va klinik qarorni yaxshilashni tekshiradi. Ko‘rilgan ishlar bu bosqichlarning turli qismlariga javob beradi. pHga sezgir fluoressent o‘choq mutlaq pH xaritasi emas; xaritaning mavjudligi esa foydali jarrohlik yoki davolash qarorini o‘z-o‘zidan tasdiqlamaydi [7, 8, 15, 18].

7.1 Ekzogen CEST-MRT bilan pH_e xaritalashning sistematik tahlili

Birinchi so‘rov 62, ikkinchisi 32 yozuv berdi. Jami 94 yozuvdan 11 aynan takror yozuv chiqarilgach, 83 noyob yozuv saralandi. Sarlavha va annotatsiya asosida 77 yozuv chiqarildi; oltita hisobot tegishli to‘liq matn bo‘limlari bo‘yicha tekshirildi. Ulardan to‘rttasi faqat hayvon yoki laboratoriya ma’lumotlarini taqdim etgani uchun chiqarildi; ikki mustaqil klinik hisobot sintezga kiritildi [7, 32]. Bu sonlar faqat qo‘shimcha modulga tegishli bo‘lib, umumiy sharhdagi 805 nomzod va 163 manbali korpus bilan qo‘shilmadi.

6-jadval. Inson o‘smalarida yodli ekzogen CEST-MRT yordamida pH_eni miqdoriy baholagan klinik hisobotlar

Hisobot va hisob birligi	O‘lchash usuli va kalibrlash	Natija va diagnostik talqin
Jones va hammualliflar, 2017 [32]. Ikki bemor: ko‘krak saratoni va tuxumdon saratoni metastazlari. Uch metastatik o‘choq bir bemorga tegishli.	3 T; iopamidol; Bloch tenglamalariga moslashtirish. Klinik xaritalar pH 6.2–7.0 bilan chegaralangan.	Metastatik o‘choqlarning o‘rtacha pH_esi 6.58; eng ishonchli natija kontrast yaxshi to‘plangan o‘choqda. Ko‘krak o‘smasida agent yetishmasligi tufayli ishonchli xarita olinmagan. Bu ikki klinik holatdan diagnostik sezgirlik hisoblanmaydi.

Hisobot va hisob birligi	O‘lchash usuli va kalibrlash	Natija va diagnostik talqin
Tang va hammualliflar, 2020 [7]. Natijalar jadvalida 15 jigar karsinomasi va 5 gemangioma bemori.	3 T; ioversol; ikki RF quvvatiga asoslangan nisbat. Maqolada e’lon qilingan fantom diapazoni pH 6.0–7.2.	Karsinoma pH_esi 6.66 ± 0.19; gemangiomada 7.34 ± 0.09. Guruhlar ajralishi istiqbolli, ammo benign guruh bahosi kalibrlash diapazonidan tashqarida. Uch tasvir chiqarilgan; ularning boshlang‘ich va yakuniy sonlarga munosabati to‘liq aniqlashtirilmagan.

Izoh. ± belgisi manbalardagi standart og‘ishni bildiradi. Ushbu hisobotlarda berilgan ko‘rsatkichlar birlashtirilgan effekt emas. Jigar ishidagi o‘rtachalar farqi 6.66 − 7.34 = −0.68 pH birligini tashkil etadi; bu manba o‘rtachalaridan olingan oddiy arifmetik tavsif bo‘lib, diagnostik chegara yoki bemorlar bo‘yicha klassifikatsiya aniqligi emas. Texnik jihatdan xarita olingan bemor ulushi ham kasallikni aniqlash sezgirligidan farq qiladi.

7.2 Diagnostik aniqlik va metodologik audit

Ikki hisobotda bemor darajasidagi to‘liq 2 × 2 jadval — haqiqiy va yolg‘on musbat, haqiqiy va yolg‘on manfiy natijalar — yoki aniqlikni qayta hisoblashga yetarli muqobil ma’lumot topilmadi. Universal chegara tashqi kohortada tekshirilmagan. Sezgirlik, spetsifiklik va AUC qayta hisoblanmadi; o‘rtacha va standart og‘ishdan taxminiy ROC chizig‘i tuzilmadi. QUADAS-3ning sonli aniqlik bahosi sharti bajarilmagani uchun 7-jadval uning domenlariga tayangan auditdir, formal baholash emas [165].

7-jadval. Klinik talqinga ta’sir qiladigan metodologik omillar

Domen	**Jones va hammualliflar** [32]	**Tang va hammualliflar** [7]
Ishtirokchilar	Tasdiqlangan saratonli klinik holatlar; benign nazorat guruhi yo‘q. Diagnostik shubhali ketma-ket bemorlar kohortasi emas.	Oldindan tashxislangan ikki guruh qiyoslangan. Barcha noaniq jigar o‘choqlaridagi ishlashiga ko‘chirish cheklangan.
Indeks test	Agent tarqalishi va xarita diapazonini chegaralash natijaga ta’sir qiladi.	Kalibrlashdan tashqari baho; B_1 bir jinsliligi tekshirilmagan.
Nishon kasallik va referens	Gistologik tashxis o‘smaga tegishli; mustaqil to‘qima pH referensi o‘rnini bosmaydi.	Karsinoma gistologik tasdiqlangan; gemangiomadagi referens va uning ko‘r-ko‘rona talqini yetarlicha bayon qilinmagan.
Tahlil	Uch o‘choqni uch mustaqil bemor sifatida hisoblash mumkin emas.	Chiqarilgan tasvirlarning guruhlar bo‘yicha oqimi noaniq.
Aniqlik bahosining mavjudligi	Bemor darajasidagi aniqlik bahosi mavjud emas; formal QUADAS-3 yakuniy hukmi qo‘yilmadi.	Bemor darajasidagi aniqlik bahosi mavjud emas; formal QUADAS-3 yakuniy hukmi qo‘yilmadi.

7.3 Dalillar ishonchliligi va metatahlil imkoniyati

Dalilning ikki savoli ajratildi: o‘lchangan pH_e guruhlar orasida farqlanadimi va test alohida bemorni to‘g‘ri tasniflaydimi? Birinchi savol uchun jigar o‘smalari qiyosi mavjud; ikkinchisiga mos sonli aniqlik bahosi yo‘q. Shu sababli 8-jadval faqat kuzatuv tadqiqotidagi biomarker farqiga moslashtirilgan GRADE profilidir. U diagnostik aniqlikka, barcha organlardagi saratonlarga yoki pH diagnostikasining umumiy foydasiga berilgan yakuniy baho emas [166].

8-jadval. Jigar karsinomasi va gemangioma orasidagi pH_e farqi uchun moslashtirilgan GRADE profili

Baholash qismi	Asos va qaror	Ishonchlilikka ta’siri
Boshlang‘ich Daraja	Bir kuzatuv tadqiqotidagi guruhlararo biomarker qiyosi; natijalar jadvalida n = 20.	Past darajadan boshlandi.

Baholash qismi	Asos va qaror	Ishonchlilikka ta’siri
Sistematik xatolik xavfi	Kalibrlash va chiqarilgan kuzatuvlar haqidagi noaniqlik o‘lchangan farqning ishonchliligiga ta’sir qiladi.	Jiddiy; bir daraja pasaytirildi.
Natijalarning izchilligi	Xuddi shu klinik qiyosni takrorlagan ikkinchi mustaqil kohorta topilmadi.	Baholab bo‘lmaydi; izchillik tasdiqlanmadi.
Bilvositalik	Bitta organdagi ikki oldindan tanlangan tashxis barcha shubhali qattiq o‘smalarni ifodalamaydi.	Keng diagnostik qo‘llanishga ko‘chirish jiddiy cheklangan.
Noaniqlik	Mustaqil validatsiya yo‘q; guruhlararo farqning ishonch oralig‘i berilmagan. Kichik nning o‘zi alohida pasaytirish mezoni sifatida olinmadi.	Qo‘shimcha daraja soni belgilanmadi.
Nashr bilan bog‘liq tarafkashlik	Bitta mos qiyos bilan statistik baholash mumkin emas.	Mavjud emas deb qabul qilinmadi.
Darajani oshirish	Kuzatilgan katta ajralish o‘lchov va tanlashdagi muammolardan mustaqil tasdiqlanmagan.	Oshirish qo‘llanmadi.
Yakuniy profil	Biomarker farqining umumlashtiriladigan kattaligiga ishonch cheklangan.	Juda past. Diagnostik sezgirlik/spetsifiklik uchun baho berilmadi.

Kiritilgan ikki hisobot birlashtirishga mos ikki diagnostik effekt bermaydi: biri klinik imkoniyatni, ikkinchisi jigar o‘smalaridagi guruhlar farqini ko‘rsatadi. pH_e uchun bitta mos qiyos mavjud, aniqlik uchun esa birlashtiriladigan baholar yo‘q. Metatahlil, I^2, funnel plot va nashr tarafkashligining statistik testi bajarilmadi. Individual bemor ma’lumoti yo‘qligi agregat ma’lumotlar metatahliliga umumiy to‘siq deb qaralmaydi.

7.4 Klinik va tadqiqot ahamiyati

Ushbu sintez pH_eni inson o‘smasida fazoviy baholash g‘oyasi klinik sharoitga o‘tkazilganini ko‘rsatadi. 3 T tizimda miqdoriy xarita olish anatomik tasvirga metabolik mikromuhit haqida qo‘shimcha axborot qo‘shish uchun asos yaratadi. pH asosidagi diagnostikaning katta imkoniyati butun organizm uchun bitta chegara izlashdan ko‘ra, muayyan organdagi aniq klinik savolga mos funksional biomarker ishlab chiqishdadir. Guruhlar orasidagi ajralish kelgusi prospektiv validatsiya uchun yo‘nalish beradi; uning alohida bemordagi qiymati tashqi tekshiruvda aniqlanadi.

Keyingi diagnostik sinovda tashxisi hali aniq bo‘lmagan ketma-ket bemorlar, bir xil klinik referens, oldindan belgilangan pH chegarasi va tasvirni ko‘r-ko‘rona talqin qilish zarur. Agent yetib bormagan o‘choqlar tahlildan yashirin chiqarilmasdan, texnik muvaffaqiyatsizlik sifatida hisobotga kiritilishi kerak. pH qo‘shilgan model odatiy MRT modeliga nisbatan bemor darajasida tekshirilib, qo‘shimcha diagnostik qiymati va klinik qarorga ta’siri baholanadi. Bu yo‘nalish pHni tasviriy diagnostikaga qo‘shish uchun aniq tekshiriladigan imkoniyatdir.

Modulning chegaralari – bitta asosiy indeks, yordamchi veb-qidiruvning barcha yozuvlar bo‘yicha alohida registrga aylantirilmagani, oldindan ro‘yxatdan o‘tgan protokol va ikki mustaqil inson baholovchi yo‘qligi. Shu sababli qidiruv doirasidan tashqarida mos ishlar qolgan bo‘lishi mumkin. Metodologik audit va moslashtirilgan GRADE profili inson ekspertlari tomonidan mustaqil takrorlanmagan. Natijalar aynan belgilangan texnologiya va vaqt oralig‘iga tegishli.

8 pHga yo‘naltirilgan davolash va klinik tatbiq imkoniyatlari

pHga sezgir tashuvchi, proton transporti ingibitori va buferlashning ta’sir mexanizmlari farq qiladi. Tashuvchi kislotalilikdan dori chiqarish signali sifatida foydalanadi; ingibitor hujayraning pH boshqaruvini

buzadi; bufer tashqi muhitni o‘zgartiradi [3, 142, 143]. Har biri uchun yetib borish, kerakli muhitdagi ta’sir, toksiklik va o‘sma nazorati tekshiriladi.

2026 yilgi erdafitinib liposomasi pH 5.3 da bir soatda 49% dori chiqargan [12]. Bu sharoit tashqi o‘sma pHining 6.5 qiymatidan farq qiladi va endosoma yoki lizosomada faollashishga mos kelishi mumkin; buning uchun lokalizatsiya dalili kerak. Formulatsiyaning preklinik natijasi erdafitinib molekulasining klinik qo‘llanishiga qo‘shilib, yangi shakl tasdiqlangandek talqin qilinmaydi.

Buferlash va transportni nishonlashning immunoterapiyaga qo‘shilgan ijobiy tajribalari mavjud [31, 126, 144, 145, 146]. Ammo esomeprazol 4T1 modelida foyda, B16-F10da yomonlashish bergan [147]. Lansoprazol va amiloridning hujayra hamda sichqondagi ta’siri mos kelmagan [148], syrosingopin bilan MCT ingibitsiyasi esa kutilgan in vivo o‘zgarishni bermagan [135]. Dori sinfi yoki pHga ta’sirning o‘zi barcha o‘smalarda samarani belgilamaydi.

Klinik AZD3965 I fazasida 40 bemorda doza va xavfsizlik baholangan, yettita dozani cheklovchi toksiklik kuzatilgan [13]. SLC-0111 I fazasidagi 17 bemorda obyektiv javob bo‘lmagan, ikki bemorda kasallik 24 haftadan ko‘proq barqaror qolgan [14]. Bu sinovlar insonda nishonlash imkoniyatini ko‘rsatadi, lekin nazoratsiz stabilizatsiyani davolash ta’siri yoki yashovchanlik foydasi deb baholash mumkin emas. Mazkur eksperimental tizimlar uchun to‘plangan dalillar rutin onkologik qo‘llanishni asoslash darajasiga yetmagan; regulyator tasdiqlar bo‘yicha alohida to‘liq audit bajarilmagan.

Metabolik monitoringning davolash javobidan farqini dixloroatsetat (DCA) tajribasi yaxshi ko‘rsatadi. TS/A o‘smalarida uch kundan so‘ng pH_e o‘zgarishi davolangan guruhda $+0.10 \pm 0.03$, nazoratda -0.12 ± 0.03 bo‘lgan; 15-kunga kelib metabolik farq susaygan [21]. Shu ishda o‘sma o‘sishi yoki hayvon yashovchanligida ishonchli foyda ko‘rsatilmagan. Demak, erta metabolik javob mavjudligi klinik samaradorlikning o‘rnini bosmaydi, ammo rezistentlikni erta kuzatish uchun qo‘shimcha axborot berishi mumkin.

Bikarbonatning fundamental sichqon ishida pH_e oshib, pH_i o‘zgarmagan va ayrim metastaz natijalari yaxshilangan, B16 modelida esa foyda bo‘lmagan [149]. Keyingi immunoterapiya bilan kombinatsiya ishida ijobiy natijalar kuzatilgan [146]; ushbu manbaning Panc02 hujayra liniyasi kelib chiqishiga tuzatish e’lon qilingan (DOI: 10.1158/0008-5472.CAN-17-0559). Bu ma’lumotlar tashqi muhitni buferlash gipotezasini qo‘llaydi, lekin bemorlarda saratonni tizimli ishqoriylashtirish bilan davolash samarasi isbotlanganini anglatmaydi.

Ayrim platformalar mahalliy kislotalashtirishni tashqi neytrallash bilan birlashtiradi. Nanokatalitik ferroptoz [150], Lipiodol Pickering emulsiyasi bilan embolizatsiya [151] va Fe/Pt elektrodlari orqali fazoviy boshqaruv [152] o‘smani shikastlash bilan immun muhitni o‘zgartirishga qaratilgan. Ularning farmakologiyasi oddiy ichiladigan buferdan farq qiladi. MRTda kuzatiladigan kislotalashtiruvchi nanoplatforma [153] ham o‘zgarishning yo‘nalishi bilan birga joyi, davomiyligi va hamroh kimyoviy jarayonlar muhimligini ko‘rsatadi.

Og‘iz orqali yuboriladigan kolorektal nanogellarda gastrointestinal tranzit va nishonga yetib borish [154], intravezikal liposomalarda ushlanib qolish va endotsitoz [12] asosiy amaliy masalalardir. Sharhlar bog‘ uzilishi, protonlanish va zaryad o‘zgarishi orqali chiqarilishni tavsiflaydi [142, 143]. Nazorat formulatsiyasi, fiziologik oqsil muhitidagi barqarorlik, chiqarilish kinetikasi va dori ekspozitsiyasi tekshirilgandagina pHga sezgirlikni samaradorlik bilan bog‘lash mumkin.

9-jadval. Terapevtik strategiyalarni qiyoslash

Strategiya va bosqich	Dalil va biologik nishon	Hal qilinmagan muammo
pH-sezgir liposoma, nanogel va peptidlar; preklinik [12, 154, 155]	Mahalliy yoki organelladagi kislotalilikda chiqarilish/faollashish	Insondagi farmakokinetika, immunogenlik, takroriy doza va tegishli pH oralig‘i.
L-DOS47; pankreatik sichqon modeli [144]	pH_e o‘rtacha +0.13; anti-PD1 javobini kuchaytirish	Kichik pH siljishining klinik ahamiyati va bemordagi nishonga ta’sir tekshirilishi kerak.

Strategiya va bosqich	Dalil va biologik nishon	Hal qilinmagan muammo
Transdermal bikarbonat; qovuq saratoni sichqon modeli [126]	Intratumoral pH va immun javobga ta'sir	Inson samaradorligi, mahalliy/tizimli xavfsizlik va ta'sir davomiyligi noma'lum.
PPI, amilorid yoki syrosingopin; eksperimental [135, 147, 148]	Proton yoki laktat/proton tashilishini o'zgartirish	In vitro–in vivo nomuvofiqlik va o'sma modeliga bog'liq yo'nalish.
AZD3965, MCT1 ingibitori; klinik I faza [13]	40 bemor; tavsiya etilgan II faza dozasi 10 mg kuniga ikki marta	Dozani cheklovchi toksiklik; samaradorlikni tasdiqlovchi nazoratli dalil emas.
SLC-0111, CAIX ingibitori; klinik I faza [14]	17 bemor; obyektiv javob 0; ikki uzoq stabilizatsiya	Kichik nazoratsiz sinov; pH farmakodinamikasi to'liq ko'rsatilmagan.
Ikki muhitli ferroptoz/immun strategiyalar; preklinik [11, 31, 150, 151, 152]	Tashqi muhit, sitozol yoki organella pH darajasini tanlab o'zgartirish	Hujayra turlari bo'yicha selektivlik, xavfsizlik va murakkab tizimni ishlab chiqarish.

8.1 Saratonsiz va saraton to'qimalarida pH farqining diagnostik va terapevtik istiqbollari

Inson to'qimalarida o'lchangan pH farqi o'smaning metabolik xususiyatlarini baholash uchun miqdoriy asos beradi. 10-jadvalda har bir saraton turi uchun ayni tadqiqotdagi saratonsiz to'qima bilan qiyos keltirilgan. Tirik organizmda olingan o'lchovlar hamda insondan ajratilgan to'qima namunalari alohida belgilandi. Bu qiyosiy sintez 7.1-bo'limdagi ekzogen CEST-MRT sistematik modulidan kengroq doirani qamrab oladi.

10-jadval. Inson organlarida saratonsiz va saraton to'qimalarining pH qiymatlari

Organ va o'sma Muhit	Saratonsiz to'qima pH	Saraton to'qimasi pH	ΔpH	Usul va manba
Miya · glioblastoma pH_i	7.04 ± 0.01 Sog'lom ko'ngillilar (n = 36)	7.12 ± 0.02 Glioblastoma (n = 16)	+0.08	In vivo ^{31}P-MRS [167]
Miya · yangi tashxislangan glioma pH_i	7.006 ± 0.012 Normal ko'ringan oq modda	7.057 ± 0.024 O'smaning butun hajmi	+0.051	In vivo 7 T ^{31}P-MRST, 12 bemor [10]
Miya · glioma pH_e bahosi	7.34 ± 0.05 Qarama-qarshi oq modda	7.44 ± 0.01 O'sma sohasi	+0.10	In vivo 7 T ^{31}P-MRST, 3 bemor [168]
Jigar · gepatotsellyulyar karsinoma pH_e	7.31 ± 0.12 O'smaga tutash parenxima	6.66 ± 0.19 Karsinoma sohasi	−0.65	In vivo 3 T ioversolli CEST-MRT, 15 bemor [7]
O'pka · bronxial o'sma pH_e	7.30 ± 0.33 Saratonsiz to'qima (n = 10)	6.46 ± 0.35 O'sma to'qimasi (n = 8)	−0.84	Ex vivo perfuziya qilingan inson o'pkasi [169]
Sut bezi · birlamchi karsinoma pH_i	≈7.3 Saratonsiz to'qima organoidlari	≈7.5 O'sma to'qimasi organoidlari	≈+0.2	Ex vivo fluoressent mikroskopiya, 1F-rasm [170]
Yo'g'on ichak · adenokarsinoma pH_i	≈7.2 Saratonsiz epiteliy kriptalari	≈7.6 adenokarsinoma kriptalari	≈+0.4	Ex vivo fluoressent mikroskopiya, 1b-rasm [171]

Izoh. ΔpH o'sma va saratonsiz to'qima uchun keltirilgan o'rtachalar ayirmasidir. ≈ bilan berilgan pH qiymatlari CO_2/HCO_3^- mavjud sharoitdagi grafiklardan taxminan o'qilgan. ± qiymatlar manbalardagi

shaklda saqlandi. Jigar parenximasining 7.31 qiymati fantomda ko‘rsatilgan 6.0–7.2 kalibrlash oralig‘idan yuqori [7]. Gliomadagi pH_e bahosiga qon fosfatining signali hissa qo‘shgan bo‘lishi mumkin [168].

Saraton diagnostikasida pH farqidan foydalanish

Jigarda o‘sma va tutash parenxima o‘rtasida kuzatilgan 0.65 birlik pH_e tafovuti anatomik MRTga metabolik xarita qo‘shish uchun asos beradi [7]. Bunday xarita tuzilishi o‘xshash o‘choqlarda to‘qimaning kislotaliligini taqqoslashga yordam berishi mumkin. Klinik sinovda pH_e qo‘shilgan MRT va standart MRT natijalari bir xil bemorlarda mustaqil referens tashxisga nisbatan qiyoslansa, mazkur signalning qo‘shimcha diagnostik qiymatini o‘lchash mumkin.

Miyada gliomaning pH_i xaritasi o‘sma ichidagi metabolik jihatdan farqli sohalarni ko‘rsatish uchun istiqbolli. Paech va hammualliflar pH_i bilan Ki-67 proliferatsiya indeksi orasida musbat bog‘liqlikni kuzatgan [10]. Bu bog‘liqlikni biopsiya joyini tanlash yoki ketma-ket MRT tekshiruvlarida o‘sma hududini kuzatish uchun sinab ko‘rish mumkin. O‘pkadagi ex vivo pH_e kontrasti esa klinik pH zondlarini ishlab chiqishga asos beradi. Sut bezi va yo‘g‘on ichak namunalaridagi pH_i o‘zgarishlari ajratib olingan to‘qimaning funksional xususiyatlarini baholash uchun alohida yo‘nalish ochadi [169, 170, 171].

Mahalliy pH korreksiyasi va davolash javobini kuzatish

Kislotali mikromuhit aniqlangan o‘smalarda pH_eni mahalliy ko‘tarish immun hujayralar faoliyatiga qulayroq sharoit yaratish uchun o‘rganilmoqda. Oshqozon osti bezi saratonining sichqon modelida o‘smaga yo‘naltirilgan L-DOS47 pH_eni o‘rtacha 0.13 birlikka oshirgan. Uni anti-PD-1 bilan birga qo‘llash anti-PD-1 monoterapiyasiga nisbatan o‘sma o‘sishini kuchliroq susaytirgan [144]. Sichqon modellaridagi buferlash tajribalari ham mahalliy atsidozni kamaytirishni immunoterapiyaga qo‘shib tekshirish uchun biologik asos beradi [146].

Sut bezi va yo‘g‘on ichak karsinomalarida pH_ining yuqoriroq saqlanishi hujayraning kislotani chiqarish tizimlarini terapevtik nishon sifatida o‘rganishga undaydi. Yangi ajratilgan to‘qimalardagi tajribalarda sut bezi karsinomasida Na^+ va HCO_3^- kotransporti, yo‘g‘on ichak adenokarsinomasida esa Na^+/H^+ almashinuvi e’tiborga molik bo‘lgan [170, 171]. O‘sma kislotaliligidan pHga sezgir dori tashuvchilarni faollashtirish uchun ham foydalanish mumkin. Bunda tashuvchining dori chiqarish diapazoni uning yetib boradigan muhitidagi pH qiymatlari bilan moslashtiriladi [12, 142, 143].

pH xaritasini davolashdan oldin va keyin takror olish aralashuvning o‘sma mikromuhitiga ta’sirini erta kuzatish imkonini beradi. Dixloroatsetat bilan o‘tkazilgan hayvon tajribasida bunday xaritalash vaqt bo‘yicha o‘zgaruvchi metabolik javobni qayd etgan [21]. Keyingi klinik tadqiqotlarda boshlang‘ich pH xaritasi bemorlarni guruhlashga, takroriy xarita esa aralashuvning nishonga ta’sirini baholashga xizmat qilishi mumkin. Ushbu o‘zgarishlarni o‘sma javobi va bemor uchun muhim yakunlar bilan bog‘lash diagnostika hamda davolash monitoringi uchun yagona tadqiqot yo‘lini shakllantiradi.

9 Kislota asos aralashuvlarining miqdoriy klinik sintezi

UBI, BiCARB va VALOR-CKD surunkali buyrak kasalligida turli vosita va yakunlarni tekshirgan [23, 24, 156]. UBIda ochiq dizayn va standart parvarish, BiCARBda yoshi katta bemorlar va jismoniy funksiya, VALOR-CKDda boshqa dori hamda kichik erishilgan bikarbonat farqi mavjud. UBIning tuzatilgan 1–3-yil dozalari 0.56, 0.55 va 0.54 mmol/kg/kun (DOI: 10.1007/s40620-020-00742-z). Natijalar ishqoriylashtirish haqidagi bitta umumiy hukmga birlashtirilmaydi.

BiCARBdagi 457 va 400 nojo‘ya hodisa hodisalar sonidir, tegishli bemorlar soni emas [24]. Kognitiv pilotdagi guruh ichidagi $p = 0.03$ natijasi platseboga nisbatan $p = 0.39$ bilan birga talqin qilinadi [157]. Siydik pH darajasining oshishi, siydik TGF-βsi o‘zgarmasligi [158] hamda veverimer metatahlilida HCO_3^- oshishi [159] biomarker yaxshilanishini organ himoyasi bilan avtomatik tenglashtirib bo‘lmasligini ko‘rsatadi.

BICARICU-2da 640 randomizatsiyalangan bemordan 627 nafari tahlil qilingan; 90 kunlik o‘lim bikarbonat va nazorat guruhlarida mos ravishda 62.1% va 61.7% bo‘lgan [160]. RRT kamayishi o‘lim natijasining o‘rnini bosmaydi. Ikki BICAR sinovining 1016 bemorli individual ma’lumotlar metatahlilida ham umumiy o‘lim RR 0.96 (95% IO 0.86–1.07), RRT boshlanishi esa RR 0.69 (95% IO 0.60–0.79) bo‘lgan [22]. RRTni boshlash qarori atsidemiya mezoniga ham bog‘liq: pHning tuzatilishi ushbu mezon bo‘yicha

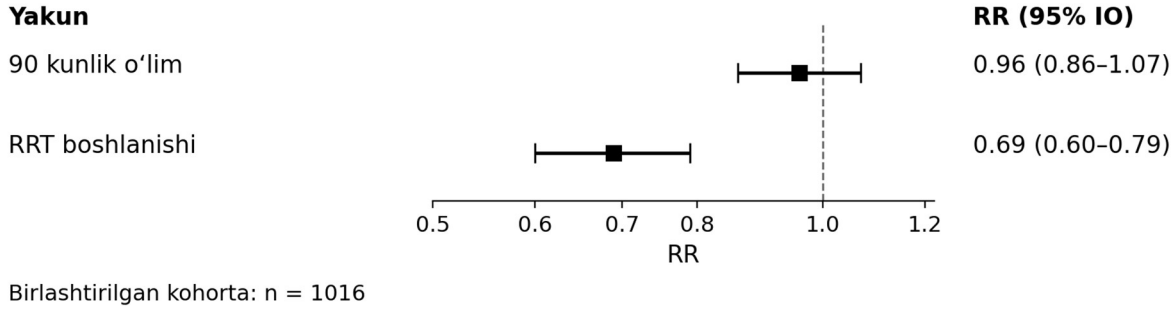
RRTga ehtiyojni kamaytirishi mumkin. Shu bois RRT kamroq boshlangani buyrak parenximasining tiklanishi yoki barcha ko‘rsatmalar bo‘yicha ehtiyoj kamayganini bevosita isbotlamaydi.

IPD metatahlilining chuqur atsidemiya kichik guruhida o‘lim RR 0.80 (95% IO 0.68–0.93), o‘zaro ta’sir p = 0.006 bo‘lgan [22]. Annotatsiya va metodlarda chegara pH ≤7.10, natijalar bo‘limida esa pH <7.10 shaklida berilgan; aynan 7.10 qiymatining guruhga kiritilishi ochiq matndan bir xil talqin qilinmaydi. Bu tafovutni muallifning ma’lumot yoki tahlil kodi asosida aniqlashtirish zarur. Guruhosti tahlili oldindan belgilangan bo‘lsa-da, mualliflar uni eksplorator deb talqin qilgan va ko‘p martalik qiyoslashga tuzatish kiritmagan. Natija keyingi tekshiruv uchun signal bo‘lib, umumiy o‘lim natijasini almashtirmaydi.

11-jadval. Kislota-asos aralashuvlarining klinik natijalari

Tadqiqot va tahlil soni	Mualliflar bergan miqdoriy natija	Qiyoslashdagi muhim farq
UBI, 2019; 740 bemor tahlili [156]	Kreatinin ikki baravar oshishi: bikarbonat 6.6%, standart parvarish 17.0%; p < 0.001	Ochiq dizayn; 795 dastlabki bemor va 740 bemor tahlili bir son emas.
BiCARB, 2020; 300 bemor randomizatsiyalangan [24]	SPPB tuzatilgan farqi −0.4; 95% IO −0.9–0.1; p = 0.15; birlamchi yakun 187 bemorda mavjud	Yoshi ≥60; jismoniy funksiya yakuni. Yo‘qolgan ma’lumot va doza UBI bilan farq qiladi.
VALOR-CKD, 2024; n = 1480 [23]	Buyrak asosiy yakuni HR 0.99; 95% IO 0.8–1.2; p = 0.90	Veverimer; guruhlar orasidagi HCO_3^- farqi ≈1 mEq/L. Bu bikarbonat bilan bevosita qiyos emas.
Sitrat–bikarbonat RCT, 2024; n = 124 [161]	eGFR farqi −0.99 mL/min/1.73 m²; 95% IO −2.51–0.93; p = 0.20. To‘xtatish: 4.8% va 17.7%; p = 0.02	Faol preparatlar qiyosi; davolamaslikka nisbatan foydani baholamaydi.
BICAR-ICU, 2018; n = 389 [162]	Birlamchi kompozit farqi −5.5 foiz punkt; 95% IO −15.2–4.2; p = 0.24	Umumiy neytral natija; AKI guruhosti signali keyingi sinovdan alohida baholanadi.
BICARICU-2, 2025; n = 627 tahlil [160]	90 kunlik o‘lim farqi +0.4 foiz punkt; 95% IO −7.2–8.0; p = 0.91. RRT farqi −15.5 foiz punkt; 95% IO −23.1–−7.8	O‘lim va RRT turli yakunlar; birini ikkinchisining o‘rniga qo‘yib bo‘lmaydi.
BICAR IPD, 2026; n = 1016 [22]	O‘lim RR 0.96 (0.86–1.07), p = 0.51; RRT RR 0.69 (0.60–0.79)	[160] va [162] bemorlarining qayta tahlili. Mustaqil uchinchi sinov emas.

Izoh: IO – ishonch oralig‘i; HR – hodisa yuz berish tezliklari nisbati; RR – nisbiy xavf; RRT – buyrak o‘rnini bosuvchi terapiya; SPPB – jismoniy funksiyani qisqa baholash testlari majmuasi. Foiz punkti ikki ulushning mutlaq farqini bildiradi. Baholar manbadan ko‘chirildi; yangi birlashtirilgan effekt yoki metatahlil hisoblanmadi. Statistik ahamiyatga erishilmagani effekt yo‘qligi yoki usullarning ekvivalentligi isboti sifatida talqin qilinmadi.



2-rasm. Ikki BICAR sinovining e’lon qilingan individual bemor ma’lumotlari metatahlilidagi 90 kunlik o‘lim va RRT boshlanishi uchun RR hamda 95% IO [22]. Baho va oraliqlar manbadan olindi; yangi metatahlil hisoblanmadi. Ikkala yakun bir xil birlashtirilgan kohortaga tegishli. RRT kamayishi o‘lim kamayishining o‘rnini bosmaydi.

10 Ziddiyatlar va metodologik cheklovlarning sintezi

Natijalar tafovuti har doim biologik ziddiyatni bildirmaydi. pH_i, pH_e va bo‘shliq pHini aralashtirish, turli kattaliklarni o‘lchash, vaqt va ta’sir davomiyligining farqi, biokimyoviy va klinik yakunlarni qiyoslash soxta qarama-qarshilik tug‘dirishi mumkin. Shu omillar tekshirilgach qolgan tafovut biologik yoki davolash samarasi haqidagi noaniqlik sifatida saqlanadi [11, 19, 22, 33, 105, 163].

12-jadval. Natijalar o‘rtasidagi ziddiyatlar, metodologik cheklovlar va tekshirish yo‘llari

Ko‘rinadigan ziddiyat	Ehtimoliy izoh va dalil holati	Hal qiluvchi tekshiruv
Gliomada pH_i yuqori; ko‘p o‘smada pH_e past [7, 10]	Turli muhitlar; biologik jihatdan birga mavjud bo‘lishi mumkin	Bir bemorda pH_i va pH_eni muvofiqlashtirilgan vaqtda o‘lchash.
MPC ingibitsiyasidan so‘ng CEST pH_e −0.22; ^{31}P-NMR sezilarli farqsiz [163]	Signal muhiti, ajratish va sezgirlik farqi; sabab yakuniy aniqlanmagan	Fazoviy moslashtirish, agent tarqalishi va bir xil muhit referensi.
Mukovissidozda ayrim ishlarda atsidoz, boshqalarida farq yo‘q [98, 99, 100, 104]	Tur, yosh, soha, dinamik tebranish va kompensator oqimlar; bir omil bilan tushuntirilmagan	Standart CO_2/namlik, kalibrlash, anatomik joy va nafas sikli protokoli.
Esomeprazol 4T1da foyda, B16-F10da yomonlashish [147]	O‘sma va immun kontekstga bog‘liqlik; universal foyda yo‘q	Bir xil doza, pH nishonga ta’siri va immun tarkibni ko‘p modelda qiyoslash.
Syrosingopin in vitro faol, in vivo pH_e va o‘sma yakuni neytral [135]	Ekspozitsiya, kompensatsiya yoki mikromuhit ehtimoli; ajratib isbotlanmagan	Farmakokinetika, intratumoral dori va transport oqimini birga kuzatish.
ONM-100 ilk natijalari yuqori, o‘pka II fazasi past [15, 18]	O‘sma turi, chekka yoki o‘choq yakuni, kamera va signal chegarasi farqi	Oldindan belgilangan bemor darajasidagi mezon va mustaqil gistologik referens.
UBI foydali, BiCARB va VALOR neytral [23, 24, 156]	Bemorlar, vosita, erishilgan farq, ko‘r dizayn va birlamchi yakunlar farqi	Yetarli biomarker ajralishi va klinik yakunli, ko‘p markazli sinov.
Bikarbonat RRTni kamaytiradi, umumiy o‘limni emas [22, 160]	Turli yakun; RRT qarori pHga bog‘liq bo‘lishi mumkin	RRT mezonlarini standartlashtirish, buyrak tiklanishi va bemor uchun muhim natijalar.
Glioma 2025 tahlili va 2024 xaritalash ishi [10, 88]	11 bemorli qayta tahlil avvalgi ma’lumotlardan foydalanadi; mustaqil kohorta emas	Bemor identifikatorlari va kiritish sanalari bo‘yicha ma’lumot manbasini ajratish.
Kichik DeepCEST RMSE, ammo o‘rtacha korrelyatsiya [8]	Tor dinamik oraliq va modelning o‘rtachaga yaqinlashtirishi ehtimoli	Mustaqil, yuqori ajratishdagi referens; diapazon bo‘yicha xato va moslik tahlili.

Jigar CEST ishida gemangioma guruhining o‘rtacha pH bahosi kalibrlash oralig‘idan tashqarida qolishi ekstrapolyatsiya noaniqligini oshiradi [7]. DOY ishida kuzatuvlarning katta qismi senzuralangani va bir bemordan takror o‘lchovlar olingani diagnostik chegaraning ishonchliligini baholashda hisobga olinishi kerak [116]. Bu cheklovlar asosiy natijalar bilan birga talqin qilinadi.

Kohorta ustma-ustligi bo‘yicha ONM-100/HNSCC juftligi tasdiqlandi [18, 136]; BICAR IPDning ikkita asosiy sinovga bog‘liqligi ham aniq [22, 160, 162]. O‘pkaning dastlabki va keyingi hisobotlari uchun bemor darajasidagi to‘liq moslik ro‘yxati mavjud ochiq dalillardan to‘liq tiklanmadi [15, 16]. Shu sababli ular mustaqil tasdiq sifatida qo‘shib hisoblanmadi, ammo to‘liq bir xil kohorta deb ham qat’iy e’lon qilinmadi.

11 Ilmiy xulosalar va kelgusi tadqiqot yo‘nalishlari

pHni muhit, vaqt va usul bilan belgilangan funksional biomarker sifatida rivojlantirish maqsadga muvofiq. Inson gliomasi, jigar o‘smasi, yara va reflyuks kuzatuvlari turli klinik imkoniyatlarni ko‘rsatadi [7, 10, 71, 116]. O‘sma atsidozining biologik asosi kuchli, biroq diagnostik yoki terapevtik qiymat o‘lchov validatsiyasi hamda bemor uchun muhim natijalar bilan tasdiqlanadi [1, 13, 14, 15, 16, 17, 18].

Keyingi tadqiqotlar uchun quyidagi gipotezalar taklif etiladi; ular ushbu sintezda isbotlangan natijalar sifatida berilmaydi.

Bir xil o‘smada pH_i/pH_e gradienti va kislotali sohalar ulushi o‘rtacha pHdan ko‘ra terapiyaga javobni yaxshiroq bashorat qilishi mumkin. Prospektiv sinovda ikkala muhit, perfuziya va nekroz bir vaqtda xaritalanib, qo‘shimcha prognostik qiymat tekshirilishi kerak.

Mukovissidozda standartlashtirilgan nafas sikli davomida pH tebranish amplitudasi statik o‘rtachadan ko‘ra himoya funksiyasiga yaqinroq marker bo‘lishi mumkin. Nazal va bronxial natijalar alohida validatsiya qilinishi lozim.

pHga yo‘naltirilgan immunoterapiya samarasi o‘sma turi bilan birga proton transporti profili, immun tarkib va boshlang‘ich pH gradientiga bog‘liq bo‘lishi mumkin. Bir xil rejim ko‘p modelda, keyin esa biomarker bo‘yicha guruhlarga ajratilgan klinik sinovda tekshirilishi kerak.

ML xaritalaridagi xato past va yuqori pH sohalarida bir xil bo‘lmasligi mumkin. Tashqi test bemor va markaz darajasida ajratilib, kalibrlash, Bland–Altman mosligi, diapazon bo‘yicha xato hamda muvaffaqiyatsiz voksel ulushi oldindan belgilanishi lozim.

Mahalliy pHni o‘zgartirishning foydasi biomarker siljishidan ko‘ra o‘sma nazorati, RRTsiz kunlar, jismoniy funksiya yoki yashovchanlik bilan baholanishi kerak. Birlamchi yakun va klinik muhim minimal farq sinov boshlanishidan oldin belgilanadi.

Standartlashtirishning amaliy yadrosi – namuna muhiti, datchik joyi, kalibrlash oralig‘i, harorat, CO_2 sharoiti, B_0/B_1 tuzatishi, kontrast dozasi, signal yetishmagan o‘lchovlar, fazoviy ajratish va vaqtni bir xil shaklda qayd etishdir. Statistik hisobotda bemor, hayvon, hujayra, kesim va voksel hisob birliklari ajratilishi, bir shaxsdan takror o‘lchovlar bog‘liqligi hisobga olinishi zarur. Bu talablar mavjud texnologiyalarni adolatli qiyoslashga xizmat qiladi.

12 Xulosa

pHni baholash o‘lchanadigan muhitni aniq belgilashdan boshlanadi. Qon, siydik, bo‘shliq suyuqligi, sitozol va organella pHlari bir-birini to‘liq ifodalamaydi. Elektrokimyoviy va optik sensorlar vaqt bo‘yicha monitoringni, MR usullari esa chuqur to‘qimaning fazoviy tahlilini kengaytiradi. Laboratoriya ajratishi, pHga sezgirlik va bemordagi mutlaq aniqlik alohida xususiyatlardir [4, 5, 7, 8, 25, 38].

pH o‘zgarishlari buyrak kasalligi, ishemiya, nafas yo‘li disfunksiyasi, fibroz, refluks va yara bitishida muhim axborot beradi. Ammo ayrim kasalliklarda o‘lchangan pH farqi topilmasligi boshqa metabolik buzilishlar mavjudligini inkor etmaydi [38, 86, 99, 100]. Muayyan aralashuvga javoban pH yoki bikarbonat ko‘tarilishi ham bemorning yashovchanligi va funksiyasi yaxshilanishini avtomatik bildirmaydi [22, 23, 24, 157, 160].

O‘sma atsidozi metabolik moslashuv, immun faoliyat, lipid olish va dori rezistentligi bilan bog‘liq. Bu biologik asos diagnostik izlanishlar uchun imkoniyat yaratadi. Kichik pilot va texnik bajarilishning o‘zi mustaqil klinik foydani tasdiqlamaydi [11, 15, 18, 123, 124, 125]. Tashuvchi, transport ingibitori va mahalliy buferlash o‘z farmakodinamikasi hamda xavfsizlik mezonlari bilan baholanadi [12, 13, 14, 31, 126].

Ekzogen CEST-MRT bo‘yicha qo‘shimcha sistematik tahlil inson o‘smasida pH_e xaritalashning klinik bajarilishi va istiqbolli guruhlararo ajralishni ko‘rsatdi. Shu bilan birga, tanlangan korpus alohida bemor uchun ishonchli diagnostik chegarani belgilashga yetmadi. Bu natija pHga asoslangan diagnostikani standart MRTga qo‘shimcha funksional biomarker sifatida, kalibrlash va tashqi validatsiya bilan rivojlantirish zarurligini asoslaydi [7, 32].

Keyingi rivojlanish umumiy kalibrlash va hisobot standartlari, bemor yoki donor bo‘yicha ajratilgan tashqi validatsiya, oldindan belgilangan fazoviy-vaqt biomarkerlari va klinik ahamiyatli yakunli nazoratli sinovlarga bog‘liq. Mavjud dalillar aniq biologik savolga javob beradigan muhitga xos pH biomarkerlarini rivojlantirishni qo‘llab-quvvatlaydi.

Adabiyotlar

F — tegishli to‘liq matn bo‘limlari; C — annotatsiya va tanlangan parchalar; A — annotatsiya; A/P — annotatsiya va mavjud preprint. Belgilar sifatni emas, manbadan foydalanish darajasini ko‘rsatadi. Asosiy [1–163] manbalar raqami saqlandi; metodologik [164–166] va qo‘shimcha to‘qima qiyoslari [167–171] kiritildi. Bibliografik yozuvlar nashr tilida, matndagi havolalar raqamli shaklda berildi. Tuzatishlar mustaqil tadqiqot deb sanalmaydi.

F — проверены соответствующие полнотекстовые разделы; C — аннотация и отдельные фрагменты; A — аннотация; A/P — аннотация и доступный препринт. Это уровень доступа, а не качество. Нумерация основных источников [1–163] сохранена; добавлены методические работы [164–166] и тканевые сравнения [167–171]. Библиографические записи сохранены на языке публикации, ссылки в тексте — числовые. Исправления не считаются независимыми исследованиями.

F indicates relevant full-text sections reviewed; C, abstract plus selected excerpts; A, abstract; and A/P, abstract plus an available preprint. These indicate access rather than quality. Core references [1–163] retain their numbering, with methods sources [164–166] and additional tissue comparisons [167–171]. Bibliographic records retain their original publication language; in-text citations are numerical. Corrections are not counted as independent studies.

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