LUNGER I PRAKSIS

MEDLEMSBLAD

03

JUNI 2023

Asthma medication adherence and exacerbations and lung function in children managed in Leicester primary care

Healthcare resources, organisational support and practice in asthma in six public health clinics in Malaysia

Asthma control among treated US asthma patients in Practice Fusion's electronic medical record research database

Modelling 30-day hospital readmission after discharge for COPD patients based on electronic health records

Care by general practitioners for patients with asthma or COPD during the COVID-19 pandemic

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FRA STYRET

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International Primary Care Respiratory Group IPCRG

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Oslo, april 2023

Kjære kollega,
Snart vår!

Astmaveileder for allmennpraksis
Lunger i praksis har fulgt opp kolsveileder for allmennpraksis med en astmaveileder. Vi har ikke noen oppdaterte veiledere for astma i Norge, noe som vi syntes ikke er holdbart. Det har skjedd mye siden NFA kom med sin i 2015. Veilederen kan du får ved henvendelse til oss.

Lungekurs Trondheim 9. - 11. mars 2023
Kurset i lungesykdommer på Britannia hotell i Trondheim ble en stor suksess! Det var over 130 deltager og gledelig at over 40 var medarbeidere!! Gode diskusjoner og mye interaktivitet preget kurset. Vi kommer tilbake til Trondheim i 2024 – samme sted!!

Lungedagene Oslo 8. – 11. november 2023
Neste mulighet for kurs blir i Oslo på Lungedagene 2023. Vi holder kurset som vanlig på Clarion Hotel Oslo, sentralt og kun et steinkast fra Sentralbanestasjonen. Som vanlig, to emnekurs fra onsdag til lørdag – og som alltid, medarbeiderkurs fra torsdag kveld til lørdag. Sett av tiden nå, mer nyheter kommer!!

IPCRG
IPCRG`s neste forskningsmøte blir i München i år, datoer er nå bekreftet til 15. og 16. mai, kanskje ikke helt ideelt for oss norske – men hvorfor ikke få litt faglig påfyll før det fylle på med pølser og is på 17. mai? Neste verdenskongress blir i Hellas i 9. - 11. mai 2024. Se også mye nyttig informasjon på IPCRG`s hjemmeside; www.theIPCRG.org

Medlemsfordeler
Mange av deltagerne på våre kurs ønsker presentasjoner fra kursene til bruk lokalt. Dette er mulig som medlem av Lip, i tillegg sender vi gjerne våre oppdaterte «Kliniske råd» til bruk i for eksempel smågrupper!
Nytt; vi har utarbeidet egne presentasjoner på astma og kols som egner seg godt til smågrupper! Ta kontakt så sender vi dem på mail! Vi har følgende kliniske råd; Spirometri, Årskontroll for astma og kols, Røykavvenning, Astma, Allergi, Kols og en for medarbeidere.
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Referanser: 1. Trimbow pulverinhalator (NEXThaler) SmPC, 2022. **2.** Buttini F, Brambilla G, Copelli D, et al. Effect of Flow Rate on In Vitro Aerodynamic Performance of NEXThaler in Comparison with Diskus and Turbohaler Dry Poweder Inhalers. J Aerosol Med Pulm Drug Deliv. 2016;29:167–17. **3.** Corradi M, Chrystyn H, Cosio B G, et al. NEXThaler, an innovative dry powder inhaler delivering an extrafine fixed combination of beclomethasone and formoterol to treat large and small airways in asthma. Expert Opin Drug Deliv. 2014;11:1497–1506.

Trimbow (beklometasondipropionat, formoterolfumaratdihydrat og glykopyrronium) Inhalasjonspulver 88 µg/5 µg/9 µg. **Indikasjon:** Vedlikeholdsbehandling hos voksne med moderat til alvorlig kronisk obstruktiv lungesykdom (kols), som ikke er adekvat behandlet med en kombinasjon av et inhalert kortikosteroid og en langtidsvirkende ß2-agonist eller en kombinasjon av en langtidsvirkende ß2-agonist og en langtidsvirkende muskarinantagonist (for effekt på symptomkontroll og forebygging av eksaserbasjoner, se SPC pkt. 5.1.). **Dosering:** 2 inhalasjoner 2 ganger daglig. Pasienten må instrueres i riktig inhalasjonsteknikk. **Pakninger og pris (AUP):** *Nexthaler inhalator:* 1×120 doser: kr 714,40. 3×120 doser: 2056,80. **Refusjonsberettiget bruk:** Vedlikeholdsbehandling ved kols, iht. preparatomtale. *ICPC/ICD:* R95/J44: Kronisk obstruktiv lungesykdom/Annen kronisk obstruktiv lungesykdom. Vilkår: Ingen spesifisert. **Reseptgruppe:** C.

Utvalgt sikkerhetsinformasjon

- Ikke indisert til behandling av akutt bronkospasme eller akutt sykdomseksaserbasjon.
- Risiko for paradoksal bronkospasme (må behandles umiddelbart), pneumoni hos kolspasienter, alvorlig hypokalemi, kardiovaskulære effekter, systemiske kortikosteroideffekter, hyperglykemi, vinkelblokkglaukom, urinretensjon, synsforstyrrelser og umiddelbar overfølsomhetsreaksjon.
- Forsiktighet skal utvises ved alvorlig nedsatt nyre- eller leverfunksjon, hjertearytmier, idiopatisk subvalvulær aortastenose, hypertrofisk obstruktiv kardiomyopati, alvorlig hjertesykdom, okklusiv karsykdom, arteriell hypertensjon, aneurisme, forlenget QTc-intervall, tyreotoksikose, diabetes mellitus, feokromocytom, ubehandlet hypokalemi, aktiv/latent tuberkulose, sopp- og virusinfeksjon i luftveiene, vinkelblokkglaukom, prostatahyperplasi og urinretensjon.
- Ved liten effekt eller sykdomseksaserbasjon, bør behandlingen revurderes. Bør ikke seponeres brått.
- Ved bruk av flere bronkodilatatorer som anfallsmedisin, bør serumkaliumnivået overvåkes.
- *Interaksjoner:* Må ikke gis samtidig med ikke-kardioselektive betablokkere eller samtidig med/de siste 12 timer før halogenerte anestetika. Langvarig samtidig bruk av andre antikolinergika anbefales ikke. Forsiktighet utvises ved samtidig bruk av potente CYP3A-hemmere, andre beta-adrenergika, legemider som kan gi hypokalemi, legemidler som påvirker nyreutskillelsesmekanismer, samtidig bruk med kinidin, disopyramid, prokainamid, antihistaminer, MAO-hemmere, TCA og fenotiaziner (gir økt risiko for ventrikulære arytmier), samt ved bruk av L dopa, L tyroksin, oksytocin og alkohol (kan hemme hjertetoleransen).
- *Graviditet og amming:* Bruk under graviditet og fødsel bør unngås. Ved inntak av anselige doser hos mor, må barnet observeres for adrenalsuppresjon. Det må besluttes om amming skal opphøre eller behandling avstås fra.
- *Bivirkninger:* Hyppigst sett er dysfoni, oral candidose, muskelspasmer og munntørrhet.

For utfyllende informasjon om dosering, kontraindikasjoner, advarsler og forsiktighetsregler, interaksjoner og bivirkninger, se Trimbow SPC godkjent 24.03.2022.

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I DETTE NUMMERET

Vi begynner denne gangen med studien til Razi Paracha og medarbeidere fra England som så på etterlevelse av inhalasjonsbehandling hos barn med astma. I England har man i mange år hatt «The quality and outcomes framework» eller QOF. Dette er en systematisk registering av kvalitetsindikatorer fra primærhelsetjenesten. For pasienter med astma registrerer man en rekke data, men etterlevelse av behandling er ikke en av dem. Man ønsket derfor å utforske sammenhengen mellom etterlevelse av inhalasjonssteroider, spirometri resultat, nivå av ekshalert nitrogenoksyd (FeNO) og astma kontroll (målt med Astma kontrolltest ACT) hos barn mellom 5 og 12 år. Barn fra tre store praksiser ble invitert til en systematisk årskontroll. Man fant 205 barn og 130 (63%) av dem møtte til kontroll. Etterlevelse inhalasjonssteroid var bare 36,4% og kun 14,6% av pasientene hadde en etterlevelse på over 75 % - som regnes som god. Selv om pasientene rapporterte god symptomkontroll viste resultatet av ACT at nær 40% ikke hadde kontroll og nær 20% hadde positiv bronkodilator responstest. Man fant imidlertid ikke noen sammenheng i denne studien mellom etterlevelse og forverringer. Forfatterne mener at dette kan forklares ved at etterlevelse ble definert ut fra apotekdata, om medisinen ble hentet ut, og ikke om medisinen faktisk ble brukt riktig. For oss understreker studien viktigheten av minst en årlig systematisk gjennomgang som vil kunne avdekke dårlig etterlevelse. Dette er et godt utgangspunkt for opplæring og kan gi økt forståelse av sykdommen.

Over de siste årene har vi hatt med mange studier fra Malaysia. Gruppen til Ee Ming Khoo (som nå er president i IPCRG) har gjort mye god forskning fra primærhelsetjenesten i et land med lite ressurser. Denne gang tar vi med studien til Norita Hussein og medarbeidere som kartla ressurser til diagnose og oppfølging av astmapasienter på seks helseklinikker i Malaysia. Klinikkene får offentlig støtte mens pasientene betaler en liten sum i egenandel (ca 2,50 norske kroner). Ved hjelp av spørreskjema kartla man klinikkene. Fire av seks klinikker hadde egne registre med oversikt over astmapasienter og alle hadde egne astmaklinikker som fulgte pasientene regelmessig ut fra behov. En klinikk hadde også et overvåkingssystem for å fange opp pasienter som falt ut av oppfølgingen. Fire av klinikkene hadde også et system for overvåking av etterlevelse ledet av en farmasøyt. Diagnose var basert på klinisk vurdering samt PEF-målinger og som regel bronkodilator responstest. Kun 18% brukte spirometri, hovedgrunnen var manglende tilgjengelighet og kompetanse til å utføre undersøkelsen. Selv om klinikkene hadde lite ressurser viser undersøkelsen at med god organisering kan man følge pasientene på en god måte. Objektive mål ved diagnose, opplæring og behandlingsplan var sentrale elementer på klinikkene, er det like bra hos oss?

Når vi er så godt i gang med studier om astma tar vi også med Jonathan Davitte og medarbeidere fra USA som så på astma kontroll i en stor database som hentet data fra over 30 000 praksiser i USA (noe som er 8% av totale praksiser!). Man hadde tilgang til astma kontrolltest (ACT) og forskrivningsdata på pasientene. Ut fra foreskrevet medisin ble pasientene kategorisert i relevante GINA alvorlighetsgrader. Resultater fra over 15 000 pasienter var tilgjengelig – snitt-alder var på 44 år og 64% var kvinner. 30% av pasientene hadde ikke god astmakontroll definert ut fra ACT-skår over 20. Det var flere av pasienter på trinn 4 og 5 med dårligere astmakontroll. Sammenlignet med andre studier viste denne studien påfallende gode resultater. Grunnen til dette mener forfatterne kan være at pasienter med ACT-skår er en selektert gruppe som sannsynligvis får bedre oppfølging! Det er det lett å være enig i – har du oversikt over ACT-skår på alle dine astmapasienter?

Så over til kols! Vi vet at det er høy risiko for komplikasjoner og død hos pasienter som blir innlagt med alvorlig kols. Mange av pasientene har hyppige innleggelser og noen er «sving-dørs» pasienter – det vil si at de blir innlagt innen 30 dager fra siste utskrivelse. Dette er et mål som er viktig, da disse pasientene nok skulle hatt tettere oppfølging og derved redusert sin risiko for nye forverringer. Meng Li og medarbeidere fra Macao i Kina ønsket i sin studie å se på risikofaktorer for reinnleggelse. Ut fra nesten 800 innleggelser fant man følgende risikofaktorer for reinnleggelse; menn over 80 år, lengden på innleggelsen, tidligere røyke historie, hemoglobin nivå, bruk av systemiske steroider og antibiotikabruk, samt tidligere innleggelser siste året. Vi vet fra tidligere studier at spesielt siste faktor er viktig. Det er derfor norske retningslinjer anbefaler en vurdering innen 4 uker etter innleggelse, på sykehus dersom pasienten har hatt respirasjonssvikt under innleggelsen, hos fastlege ellers!! Husk alltid å kartlegge forverringer siste året ved kontakt med kolspasienter!

Til slutt tar vi med en studie fra Corinne Rijpkema og medarbeidere fra Nederland. Studien så på oppfølging og behandling av astma og kols under pandemien og viser interessante tall. Data fra allmennlegekontorer og legevakt ble samlet inn, og man ønsket å kartlegge hvordan konsultasjoner varierte i løpet av pandemien, hvordan kontaktene fant sted og i hvilken grad akutte konsultasjoner endret seg fra før pandemien. Som nok mange av oss i Norge også erfarte var det en markert nedgang i fysiske kontakter under pandemien. Man fant også økt antall telefonkonsultasjoner. Legevaktkontakter viste også betydelig og vedvarende økning i telefonkonsultasjoner. Imidlertid så man en nedgang i antall akutte kontakter på legevakt. Mye av dette mener forfatterne kan forklares av lavere forekomst av smittsomme sykdommer grunnet smittetiltak, men også at pasientene ikke tok kontakt da de ikke ønsket å belaste en presset helsetjeneste. Det at nedgangen ikke bare var på legekontor, men også på legevakt, overrasket forfatterne. Man hadde forventet flere akutt syke pasienter siden vanlige kontroller hos fastlegen uteble. Årskontrollene på legekontoret forventer vi jo skal bedre oppfølging og redusere forverringer. Videre forskning vil avdekke om man vil se en økning i innleggelser i tiden som kommer.

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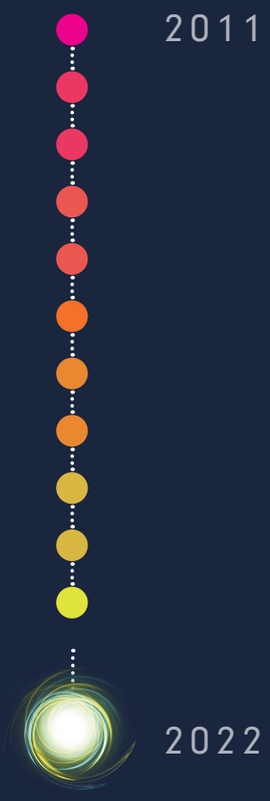

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INDIKASJON: Aktiv immunisering for forebygging av invasiv sykdom og pneumoni forårsaket av Streptococcus pneumoniae hos personer fra 18 år og eldre.

Referanse: 1. APEXXNAR SPC, 01.12.2022

▼Apexxnar sikkerhetsinformasjon:
Kontraindikasjoner: Overfølsomhet for innholdsstoffene eller difteritoksoid. **Forsiktighetsregler**: Egnet medisinsk behandling og overvåkning skal alltid være tilgjengelig i tilfelle anafylaktisk reaksjon. Vaksinen må administreres med forsiktighet hos personer med trombocytopeni eller blødningsforstyrrelse. **Interaksjoner**: Ingen interaksjonsstudier har blitt utført. Forskjellige injiserbare vaksiner skal alltid gis på ulike injeksjonssteder. Apexxnar kan administreres samtidig med covid-19 mRNA-vaksine (nukleosidmodifisert).**Dosering og administrasjonsmåte:** 1 dose (0,5 ml) settes intramuskulært, fortrinnsvis i deltamuskelen. Apexxnar skal ikke injiseres intravaskulært. **Viktige bivirkninger:** Overfølsomhetsreaksjoner, anafylaktisk/anafylaktoid reaksjon inkludert sjokk er rapportert, se også Forsiktighetsregler. **Pris**: 1 stk 997,20 kr, suspensjon i ferdigfylt sprøyte uten kanyle. APEXXNAR kan rekvireres av lege på blå resept direkte fra Folkehelseinstituttet med henvisning til §4 for utvalgte pasientgrupper, herunder pasienter uten miltfunksjon, HIV positive personer og personer som har gjennomgått stamcelletransplantasjon. Reseptgruppe C.

Prevenar13 sikkerhetsinformasjon
Indikasjon: Aktiv immunisering for foreygging av invasiv sykdom og pneumoni forårsaket av Streptococcus pneumoniae hos voksne ≥18 år og hos eldre. Bruk av preparatet bør baseres på offisielle anbefalinger. Dosering voksne ≥ 18 år: En enkeltdose gis ved intramuskulær injeksjon. **Kontraindikasjoner**: Vaksinasjon skal utsettes ved akutt, alvorlig febersykdom. Mindre infeksjoner som forkjølelser skal imidlertid ikke gjøre det nødvendig å utsette vaksinasjonen. Kontraindisert ved overfølsomhet for virkestoffene eller difteritoksoid. **Forsiktighetsregler**: Egnet medisinsk behandling og overvåkning skal alltid være tilgjengelig i tilfelle sjeldne anafylaktiske reaksjoner oppstår etter injeksjon. **Interaksjoner**: Prevenar 13 kan gis samtidig med sesongens kvadrivalente, inaktiverte influensavaksine (QIV). **Viktige bivirkninger:** Overfølsomhetsreaksjoner, anafylaktisk/anafylaktoid reaksjon inkludert sjokk er rapportert, se også Forsiktighetsregler. **Pris**: 698,20 kr. Reseptgruppe C.

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PERSPECTIVE OPEN

Check for updates

Asthma medication adherence and exacerbations and lung function in children managed in Leicester primary care

Razi Paracha[1]✉, David K. H. Lo[2,3], Ursula Montgomery[4], Louise Ryan[4], Vivek Varakantam[5] and Erol A. Gaillard[2,3]

Poor adherence to asthma preventer medication is associated with life-threatening asthma attacks. The quality and outcomes framework mandated primary care annual asthma review does not include adherence monitoring and the effect of poor adherence on lung function in paediatric primary care patients is unknown. The aim was to investigate the link between inhaled corticosteroid (ICS) adherence and spirometry, fraction of exhaled nitric oxide (FeNO) and asthma control in asthmatic school-age children in this cross-sectional observational study involving three Leicestershire general practices. Children 5–16 years on the practice's asthma registers, were invited for a routine annual asthma review between August 2018 and August 2019. Prescription and clinical data were extracted from practice databases. Spirometry, bronchodilator reversibility (BDR) and FeNO testing were performed as part of the review. 130 of 205 eligible children (63.4%) attended their review. Mean adherence to ICS was 36.2% (SEM 2.1%) and only 14.6% of children had good adherence (≥75% prescriptions issued). We found no differences in asthma exacerbations in the preceding 12 months between the adherence quartiles. 28.6% of children in the lowest and 5.6% in the highest adherence quartile had BDR ≥ 12% but this was not statistically significant ($p = 0.55$). A single high FeNO value did not predict adherence to ICS. Adherence to ICS in children with asthma in primary care is poor. The link between adherence to ICS and asthma exacerbations, spirometry and FeNO is complex but knowledge of adherence to ICS is critical in the management of children with asthma.

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INTRODUCTION

UK children with asthma have the highest rate of severe asthma attacks of any high-income country in Europe[1]. Over 150,000 children have severe asthma attacks each year[2], and 26,000 require hospital admission[3], the equivalent of one child being admitted to a UK hospital every 20 min. These figures have changed little over the last two decades and this is identified as a health priority in the 2019 NHS long-term plan[4].

Most UK children with asthma are managed in primary care. Asthma management in primary care is largely symptoms-based[5] and relies on the Royal College of Physician three questions (RCP3Q) symptom score, which is less useful in children[6]. Importantly, only a third of patients receive an adequate asthma review in primary care[7] and reviews frequently do not involve formal adherence monitoring.

Adherence to preventer medication and inhaler technique is often poor[8–10]. A recent systematic review, which included mostly US studies, highlighted the association between poor adherence and a higher risk of severe asthma attacks[11]. In the UK, poor adherence to asthma medications has also been associated with an increased risk of life-threatening asthma attacks as demonstrated in the 2014 National Review of Asthma Deaths (NRAD), where over one-third of patients who died were prescribed less than 25% of their required ICS inhalers[12].

Both, poor lung function and elevated FeNO are associated with an increased risk of asthma attacks[13,14]. There is no data on the link between adherence to preventer medication and objective measures of lung function and airway inflammation in children managed in UK primary care.

The aim of this study was to investigate the link between adherence to preventer asthma inhaler medication and spirometry, bronchodilator reversibility (BDR) and FeNO results in children aged 5–16 years managed in UK primary care.

METHODS

Design and setting

This observational cross-sectional study took place across three primary care practices in Leicestershire, UK; between August 2018 and August 2019. These three practices were chosen as they were already part of a local innovative quality improvement Fellowship Programme. Ethical approval was not required.

Participants

Children aged 5–16 years with a recorded diagnosis of asthma on the practice register and prescribed regular inhaled corticosteroids were eligible for inclusion in the study.

Eligible patients were invited for their routine annual asthma review by telephone call or letter. The project was conducted as a quality improvement project in primary care. Written informed consent was obtained. Each clinical review was conducted in line with established UK asthma guidelines. There was no randomisation and no identifiable data collection and therefore, no Research Ethics Committee approval was required.

Practice database searches

Searches to identify patients on the asthma register were performed across all three practices in Leicestershire using the SystmOne computer system by the practices themselves. Patient electronic records were interrogated to obtain details of asthma attacks in the previous 12 months and to collect adherence data

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based on the number of asthma medication prescriptions issued over the previous 12 months.

Asthma attacks were defined as an unscheduled healthcare consultation or any hospital attendance with acute wheezing with or without a prescription of systemic corticosteroids.

Adherence data

The adherence rate was calculated as the ratio of doses of medication issued and a total number of doses in the intended treatment regimen, expressed as a percentage. This method of adherence measurement has been described in previous studies as a "medication possession ratio"[11]. An adherence ratio of ≥75% was considered to be good adherence[15]. The maximum adherence ratio was capped at 100%.

Asthma reviews

All asthma reviews included an assessment of asthma symptom control, checking of inhaler technique, an update of the personalised written asthma action plan, and lung function testing.

Regular asthma medications were not withheld on the day of review.

Asthma control

During the face-to-face consultation, parents and the child were asked to complete an asthma control test (ACT)[16] if ≥12 years old and the Children's cACT[17] if <12 years. A score of <20 for either test was considered to indicate poor control.

Fractional exhaled nitric oxide

The fraction of exhaled nitric oxide (FeNO*)* was measured using a near-patient electrochemical analyser (NIOX VERO®, Circassia Group, Oxford, UK). FeNO was always tested prior to spirometry. The value taken was from the first successful attempt that achieved the sustained flow rate required[18]. A FeNO value ≥35 ppm was taken as the cut-off value for abnormally raised FeNO[19].

Spirometry

Spirometry was performed by the quality improvement project fellow using a MicroLab Mk8 flow turbine spirometer (CareFusion, San Diego, CA, USA). Forced expiratory manoeuvres were performed according to American Thoracic Society and European Respiratory Society (ATS/ERS) standards[20]. BDR testing was performed after administering 400 micrograms of salbutamol inhaler via a spacer device. BDR was tested in all patients performing spirometry. Lung function parameters were expressed as percentage predicted for FEV_1 and FVC, and as the absolute percentage for FEV_1/FVC. The Global Lung Initiative (GLI) 2012 reference equations were used[21].

Data analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows (Version 24.0. Armonk, NY: IBM Corp) and GraphPad Prism version 7.00 for Windows (GraphPad Software, USA, www.graphpad.com).

Continuous variables were compared using unpaired *t*-tests for parametric data, and Kruskal–Wallis and Wilcoxon rank-sum tests for non-parametric data. Chi-squared tests were used for count data.

All statistical tests were performed at the alpha = 5% level.

Reporting summary

Further information on research design is available in the Nature Research Reporting Summary linked to this article.

RESULTS

The 3 primary care practices were of similar size (registered patients ranging from 8200 to 9200), and in the 6th, 9th and 10th deciles of deprivation (Table 1). The first decile represents the most deprived areas, and the tenth is the least deprived areas[22].

We identified 245 children with an asthma diagnosis code. Of these, 205 were on regular inhaled corticosteroids as part of their asthma treatment and all were invited for a review. 130 out of 205 (63%) attended. Spirometry was attempted in all children, and useable data were obtained from 116 (89%). FeNO equipment was not available at the start of our study but was available for 96 out of 130 children. FeNO was successful in 65 (68%) children (Fig. 1).

Mean (SEM) adherence in the 205 children eligible for participation was found to be 36.2% (2.1%). Only 14.6% of patients had a target adherence rate of ≥75% (quartile 4) (Table 2).

Forty-nine patients out of 130 (37.7%) had poor control according to their ACT/cACT score. 18% had significant bronchodilator reversibility on spirometry and 55% of the total patients had raised FeNO > 35 ppb.

Relationship between adherence, spirometry, FeNO and asthma control

Lung function, FeNO and asthma control data for the 130 children attending for review are shown in Table 2.

The relationship between adherence and asthma symptom scores is plotted for each patient in Fig. 2.

We found no significant differences in symptom scores, FEV_1, FEV_1/FVC, or FeNO between the different adherence categories (Table 2).

There was a trend towards fewer children with a positive BDR ≥ 12% with increasing adherence ($p = 0.143$). In total, 28.6% of children with the poorest adherence (Q1) had BDR > 12% compared to only 5.6% of children with the best adherence (Q4), however, this did not reach statistical significance ($p = 0.055$).

Relationship between ICS adherence, ethnicity, SABA usage and asthma exacerbations

Seventeen children (8%) had had at least one asthma exacerbation in the previous year. We found no difference in the mean number of attacks between children in different adherence quartiles. We found a significant difference in the number of SABA prescriptions between ICS adherence quartiles, with the fewest number of SABAs prescribed to children with the lowest ICS adherence (Table 3).

We found no significant differences in adherence rates between children from different ethnic backgrounds (Table 4).

Table 1. Practice demographics.

	Registered patients	Decile of deprivation index	White %	Asian %	Black %	Other %	Mixed %
Practice 1	8877	9th	62.1	31.7	1.5	2.2	2.5
Practice 2	9254	10th	56.2	37.3	1.5	2.6	2.4
Practice 3	8276	6th	91.4	5.1	0	1.3	2.2

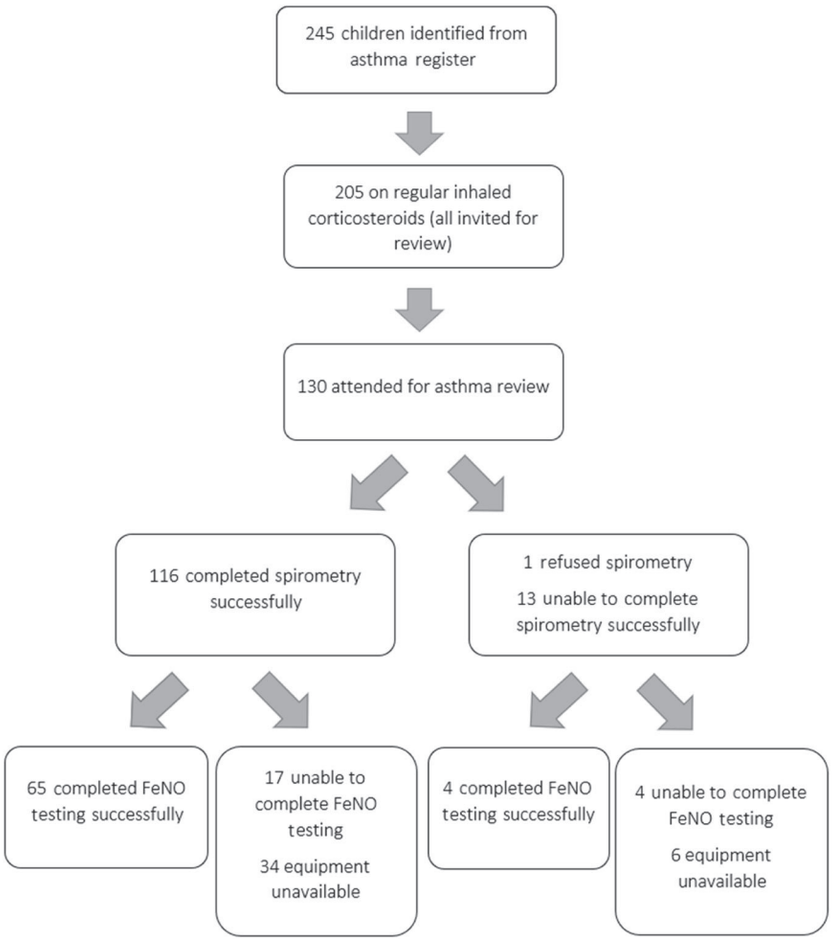

Fig. 1 Eligibility and follow-up of children with asthma. Children were invited to attend for an asthma review at their general practice that included spirometry, bronchodilator reversibility and fraction of exhaled nitric oxide (FeNO) testing.

DISCUSSION

Several previous studies and a systematic review reported low adherence to asthma-preventer inhaler medication in children followed up in primary care[8–11,23]. The mean adherence of 36.4% in our cohort of children was also low, and >75% adherence in only 14.6% of patients. A target adherence rate of ≥75% was used as this has been shown to significantly improve asthma control[15,24,25]. The aims of asthma management are to achieve good symptom control and minimise the risk of future asthma attacks and identify the lowest dose of inhaled corticosteroids needed to achieve these goals[5,26]. Although many patients report "good symptom control", there is discordance between the symptoms reported and objective data[11,27]. Previous studies have reported the connection between low lung function and higher morbidity[13,28,29].

Our study offers novel insights into the relationship between preventer medication adherence, asthma control and objective measures of lung function and airway inflammation. The complex link between ICS adherence and asthma exacerbations, spirometry, BDR and FeNO is highlighted in this study. Overall, we found no significant differences in lung function, FeNO and ACT scores between the adherence quartiles. This finding highlights that children with asthma are a heterogeneous group. Objective measures of lung function and airway inflammation; combined with the knowledge of asthma symptom control and adherence, provide a much more granular picture to allow the formulation of an effective management strategy. This strategy can then be tailored to the needs of the individual child, providing truly personalised medicine. This is not possible when relying on asthma symptom control alone.

BDR, for example, is a marker of airway lability and is associated with poor asthma control[30]. Nearly 30% of children in our lowest adherence quartile showed BDR > 12%, more than in the highest adherence quartile ($p = 0.055$). In fact, 20 of 82 children (24.4%) with <50% adherence demonstrated bronchial lability. These children have active asthma and are likely undertreated, and these patients require intervention towards better adherence. This is also reflected in the finding of the highest median FeNO values in the lowest two quartiles.

In contrast, most children in the lower two adherence quartiles had good symptom control, no significant BDR, and minimal or no use of preventer medication and these children either do not have asthma or do not have active asthma. With evidence of good lung function, these children would merit a trial of formally stopping ICS treatment (step-down treatment).

Only three of 41 children with adherence ≥50% showed BDR ≥ 12%, showing that airway lability is reduced with regular ICS treatment. Children with significant BDR despite regular ICS should be considered for a trial of long-acting beta-agonist treatment (step-up treatment).

A number of children in the highest adherence quartile, indeed a number of these picking up 100% of their prescriptions, remained uncontrolled. We do not know whether these children actually took their inhalers as directed, but once treatment has

Table 2. Patient characteristics and clinical information.

All patients invited for review ($n = 205$)	
Number of males (%)	116 (56.6%)
Median age (IQR)	10 (8–13)
Ethnicity (%)	
White	92 (44.9)
Black	9 (4.4)
Asian	72 (35.1)
Other/mixed	32 (15.6)
Adherence	
Quartile 1–0 to 24%	74 (36.1)
Quartile 2–25 to 49%	72 (35.1)
Quartile 3–50 to 74%	29 (14.1)
Quartile 4–75 to 100%	30 (14.6)
All patients attending ($n = 130$)	
Males (%)	79 (61)
Median age (IQR)	9 (8 to 12)
Adherence	
Quartile 1–0 to 24%	38 (29.2)
Quartile 2–25 to 49%	49 (37.7)
Quartile 3–50 to 74%	22 (16.9)
Quartile 4–75 to 100%	21 (16.2)
Median asthma control score (IQR)	
CACT	21.5 (19–24)
ACT	20.0 (16.75–23)
Number of patients with ACT/cACT <20 (%)	49 (37.7%)
Mean FEV_1 % Predicted (SEM)*	93.3 (1.17)
Mean FEV_1 *z*-score (SEM)*	−0.56 (0.10)
Mean FEV_1/FVC (SEM)*	0.90 (0.01)
Mean FEV_1/FVC *z*-score (SEM)*	0.45 (0.13)
Number of children with BDR ≥ 12% (%)*	21 (18.1%)
Median FeNO (IQR)**	38 (13–56)
Number of children with FeNO ≥ 35 ppb (%)	36 out of 65 (55.1%)

	Adherence quartile				
	Quartile 1 (0–24%) $N = 38$	Quartile 2 (25–49%) $N = 49$	Quartile 3 (50–74%) $N = 22$	Quartile 4 (75–100%) $N = 21$	*P* value
Median ACT (IQR)	21 (18.5–23.5)	20 (15.5–22.5)	19(17–24)	17 (10.5–21)	0.381
Median CACT (IQR)	21 (19–24)	21 (17–24)	21 (19–23)	23 (16–24)	0.972
Mean FEV_1 % Predicted (SEM)[a]	93.9 (2.57)	91.3 (1.85)	95.1 (2.49)	95.1.8 (2.70)	0.560
Mean FEV_1 *z*-score (SEM)	−0.52 (0.21)	−0.72 (0.15)	−0.40 (0.20)	−0.41 (0.22)	0.544
Mean FEV_1/FVC (SEM)[a]	0.90 (0.01))	0.90 (0.01)	0.88 (0.02)	0.93 (0.01)	0.306
Mean FEV_1/FVC *z*-score (SEM)[a]	0.39 (0.29)	0.57 (0.22)	−0.00 (0.29)	0.80 (0.24)	0.301
Number of children with BDR ≥ 12% (%)[a]	8/28 (28.6%)	10/48 (20.8%)	2/22 (9.1%)	1/18 (5.6%)	0.143
Median FeNO (IQR)[b]	46.5 (17–56)	46 (10–75.75)	18 (12.25–39.5)	36 (14–48)	0.352
Number of children with FeNO ≥ 35 ppb (%)[b]	12/18 (66.7%)	15/28 (53.6%)	4/10 (40%)	5/9 (55.6%)	0.589

[a]Spirometry and BDR data available from 116 children.
[b]FeNO from 65 children.

been escalated to moderate dose ICS plus LABA and control remains poor, these children warrant referral to a specialist paediatric asthma service.

NICE recommends the use of spirometry to support asthma monitoring and management[19]. Our study shows that using spirometry and BDR in cases where baseline spirometry is abnormal i.e., where FEV_1 and/or FEV_1/FVC is/are below the lower limit of normal (GLI reference) identified the 18.6% of children with significant BDR, most of whom were in the lower two adherence quartiles. These children have reactive airway disease and are at risk of an asthma attack. This would also strengthen the education of families and children with asthma by showing

objective evidence of poor control in the form of lung function tracings.

During the asthma reviews, the adherence rate, asthma control score and objective testing results were all discussed with the patient and parent. A targeted management plan was then formulated. If poor disease control was associated with poor adherence, then treatment was not stepped up and adherence counselling was carried out instead (with follow-up). Similarly, if disease control was good despite poor adherence, treatment could be stepped down. An alternative diagnosis was considered for those with normal objective testing and ongoing symptoms. There is also an opportunity to identify patients with high BDR or FeNO with good subjective symptom control, as these patients may be at risk of severe exacerbations with uncontrolled active disease.

The areas included in the study have a significant minority ethnic population (especially South Asian), and comparing adherence between ethnic groups found no significant difference. Ethnic disparities in the use of asthma controller medication have been reported[31,32]. We found no differences in the adherence to ICS between Black, Asian and White children in our study, suggesting that the reasons for non-adherence are independent of ethnicity.

Accurate prescription data was collected for the 12 months immediately prior to the consultation and respiratory testing.

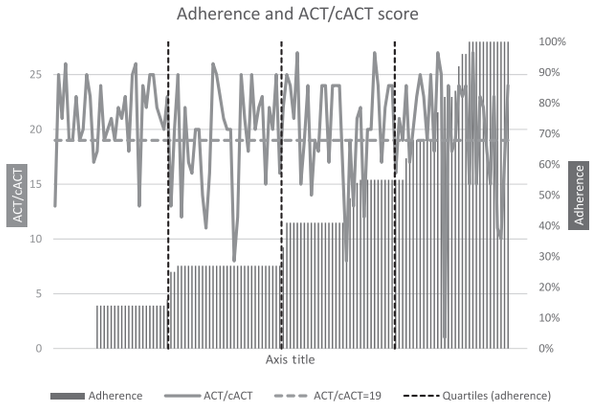

Fig. 2 Relationship between adherence and ACT/cACT score plotted for all 130 patients each blue bar represents the adherence of one patient. The grey dotted horizontal line represents an ACT/cACT score of 19. A score <20 represents poor symptom control. The black dotted vertical lines represent quartiles of adherence.

Prescription data gives a much more objective measure of adherence than subjective patient/parental reporting (precluding recall bias)[33]. Outcome measures were also carried out with the validated ACT/cACT questionnaires and objective testing with spirometry and FeNO. This gives us better data than other database studies in which there is little data about asthma severity. In our searches, no similar studies were found in primary care relating adherence to objective testing.

As asthma is a difficult diagnosis, especially in children, we attempted to include patients who may not have been coded correctly on the primary care practice database by including children who had been prescribed 2 or more SABA or preventer inhalers over the past year due to wheeze (and no other established respiratory diagnosis).

Attenders may be a self-selected population and may be more proactive with their disease management. The cohort attending for review had higher adherence compared to those who did not (Table 2). Additionally, the patient population may be a very heterogenous group e.g., quartile 1 might include dormant asthma, those misdiagnosed, as well as patients who are extremely non-adherent. This may contribute to the complex relationships in the data above.

The medication possession ratio is an indirect measure of adherence. This does not tell us if the medication was actually used or properly administrated. Although, this is a pragmatic approach that can be used in current clinical practice without investment into additional measures such as "smart" inhalers. There is evidence that healthcare database information can provide high concordance with other accurate and objective methods such as weighing inhalers or electronic monitoring[34,35].

Significant challenges exist in adopting lung function testing in primary care.

FeNO equipment was not available during the first part of the study and the test was therefore only available for 69% (90 out of 130) of the study population. There are no previous data that allowed us to perform a meaningful power calculation, and the power of this study is limited by the number of patients, especially with the small number of patients with successful FeNO testing. Raised FeNO is associated with classical, steroid-responsive, type-2 airway inflammation. Raised FeNO is also present in children with other atopic diseases, such as allergic rhinitis and eczema. Due to the cross-sectional observational nature of this study, we cannot be sure that the raised FeNO observed in some patients are due to uncontrolled airway type-2 inflammation. High FeNO values ≥ 35 ppb were observed in all 4 adherence quartiles.

Table 3. Relationship between ICS adherence with SABA usage and attacks over the 12-month observation period in all children invited for a review ($n = 205$).

	Preventer adherence quartiles				*P* value
	Quartile 1 (0–24%)	Quartile 2 (25–49%)	Quartile 3 (50–74%)	Quartile 4 (75–100%)	
Mean number of attacks (SEM)	0.08 (0.03)	0.06 (0.03)	0.17 (0.07)	0.10 (0.07)	0.362
Mean number of SABA inhalers/year (SEM)	1.55 (0.25)	4.15 (0.37)	4.66 (0.77)	4.20 (0.53)	<0.001

Table 4. Relationship between ICS adherence and ethnicity in all children invited for a review ($n = 205$).

	Ethnicity				*P* value
	White	Black	Asian	Other/mixed	
Mean adherence (SEM)	0.36 (0.03)	0.36 (0.10)	0.39 (0.04)	0.30 (0.05)	0.615

We found no published evidence showing the relationship between adherence and objective testing in children in primary care.

Low mean adherence in our population was consistent with that reported in other studies[11,36,37]. This continues to be extremely poor and shows significant room for improvement in addressing poor outcomes for asthmatic children in the UK.

SABA prescriptions increased with increasing preventer adherence. This has been demonstrated previously[36] and suggests a complex relationship. Inhaler use may be self-regulated and those with increasing symptoms may be increasingly adherent to preventers while also needing more SABA, suggesting symptom control is still inadequate.

Previous studies examine the relationship between adherence and asthma exacerbations[36–38], but none have established the relationship between adherence and objective measures of asthma control. Our data show exacerbations are evenly distributed across the quartiles. Worsening spirometry and FeNO can be better indicators of worsening asthma severity[27,39]. Adherence and objective testing together can provide valuable clinical information, but we need a clearer picture of how adherence is related to disease outcomes.

Effective treatments for asthma are available, yet many children's asthma still remains uncontrolled[27]. Factors such as trigger identification, comorbidities and asthma phenotype, as well as clinician and sociodemographic factors, play an important role[40]. Poor adherence to ICS treatment is an important contributory factor to poor asthma control that can be fairly easily identified, although changing family and child behaviour can be challenging[41,42]. However, the identification of poor adherence is an important first step.

Although the relationships between adherence and indicators of asthma control may be complex, prescription data can provide useful information during primary care consultations. Clinically a practitioner would be able to use adherence information to better target changes in treatment. A child with suboptimal asthma control would need different interventions depending on whether the medication adherence is adequate or not, as stepping up treatment does not address the infrequent use of the medication. The method we have used to review adherence data is instantly accessible to GPs using the SystmOne computer system (currently widely used in the UK), and can easily be accessed during asthma review consultations within the appointment time.

We know that misdiagnosis of asthma in children is common[43,44]. Large numbers of children are over-diagnosed with asthma and these children would not be expected to respond to asthma-preventer medication; hence the poor adherence. This highlights the need for more objective testing to confirm the diagnosis in children.

Considering that patient-reported adherence and control can be very inaccurate, this also supports the increasing role of routine objective testing in primary care. Patients can perceive that their asthma is well controlled, when in fact, objective testing proves otherwise. NICE asthma guideline recommendation for using objective testing does pose a significant challenge with regard to training and time constraints in primary care. In practice, any patient with poor symptom control or abnormal objective testing should have confirmation of the diagnosis and a structured review and follow-up plan until control is achieved[40].

In summary, more data is needed to establish the relationship between adherence to asthma medication and asthma control (not just exacerbations). The heterogeneity of the patient populations may pose a challenge as it is difficult to discern those who are taking less medication because their symptoms are adequately controlled, from those who do not adhere to their medication regimen resulting in worsening disease control. The impact of reduced adherence and clinical management will be very different in both these groups.

DATA AVAILABILITY

The data that support the findings of this study are openly available in Figshare at https://doi.org/10.6084/m9.figshare.21598836.v1.

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AUTHOR CONTRIBUTIONS

R.P.—Lead author. Study design, planning, patient consent, data collection, patient clinical review and lung function testing, statistical analysis, manuscript authorship and review. D.K.H.L.—Study design, planning, equipment training, statistical analysis, paper authorship and review. U.M.—Study design, planning, patient identification, organising logistics at the patient testing sites, paper authorship and review. L.R.—Study design, planning, patient identification, organising logistics at the patient testing sites, paper authorship and review. V.V.—Study design, planning, patient identification, organising logistics at the patient testing sites, paper authorship and review. E.A.G.—Study design, planning, equipment training, statistical analysis, paper authorship and review.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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Behandlingen (2 ganger daglig i 5 dager) bør starte umiddelbart etter en positiv covid-19 test og ≤ 5 dager etter symptomdebut[1]

88% Relativ risikoreduksjon for sykehusinnleggelse eller død vs. placebo i EPIC-HR studien[2*]

Referanser: 1. PAXLOVID SPC **2.** Hammond J, Leister-Tebbe H, Gardner A, et al. Oral nirmatrelvir for high-risk, nonhospitalized adults with covid-19. *N Engl J Med*. 2022;386(15):1397-1408.
*Hos pasienter som fikk behandling innen 5 dager etter symptomdebut, og som ikke fikk behandling med monoklonalt antistoff ved baseline, ble den absolutte risikoen for sykehusinnleggelse eller død redusert fra 6.4% til 0.78%, dvs med 5.62 prosentpoeng (95 % KI = -7.21, -4.03), p<0.001.

Indikasjon: PAXLOVID® er godkjent for behandling av covid-19 hos voksne som ikke har behov for supplerende oksygenbehandling, og som har økt risiko for å utvikle alvorlig covid-19 sykdom.[1]

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Healthcare resources, organisational support and practice in asthma in six public health clinics in Malaysia

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Asthma, a common chronic respiratory illness is mostly managed in primary care. We aimed to determine healthcare resources, organisational support, and doctors' practice in managing asthma in a Malaysian primary care setting. A total of six public health clinics participated. We found four clinics had dedicated asthma services. There was only one clinic which had a tracing defaulter system. Long-term controller medications were available in all clinics, but not adequately provided. Resources, educational materials, and equipment for asthma management were present, though restricted in number and not placed in main locations of the clinic. To diagnose asthma, most doctors used clinical judgement and peak flow metre measurements with reversibility test. Although spirometry is recommended to diagnose asthma, it was less practiced, being inaccessible and unskilled in using as the main reasons. Most doctors reported providing asthma self-management; asthma action plan, but for only half of the patients that they encountered. In conclusion, there is still room for improvement in the provision of clinic resources and support for asthma care. Utilising peak flow metre measurement and reversibility test suggest practical alternative in low resource for spirometry. Reinforcing education on asthma action plan is vital to ensure optimal asthma care.

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INTRODUCTION

Asthma is the most common chronic respiratory illness affecting an estimated 262 million people worldwide[1]. In Malaysia, the prevalence is estimated between 8.9 and 13.0% in children[2,3] and 6.3% in adults[4]. Despite evidence-based asthma management recommendations and treatments, asthma control is still sub-optimal. A recent local study showed only 37% had well-controlled asthma, 36% were partly controlled and 27% uncontrolled[5]. Primary care is ideally placed to diagnose, manage and provide continuous care to patients with asthma[6,7]. Important factors that have been reported to facilitate improvement in primary care management of asthma include availability of good organisational support and access to resources within the practice, as well as having a dedicated asthma team (doctors, pharmacists, nurses, allied health professional trained in asthma)[8]. However, it is not clear to what degree these factors are being provided to facilitate asthma management in our Malaysian primary care setting. We therefore aimed to determine current resources available, organisational support and doctors' provision of asthma care in our public health clinics. The findings will help inform strategies to improve the delivery of asthma care in our setting.

METHODS

Study design, setting and participants

This is a cross-sectional survey conducted from December 2019 to January 2020 in six public health clinics in Klang District, Malaysia. Malaysia has a dual-sector healthcare system: public and private sectors[9]. The public health clinics are government-funded with heavily subsidised in which patient pays MYR1 (USD0.24) per clinic visit that covers the cost of consultation, investigations, and medications while government employees, pensioners, school-going children and people aged 60 years and above receive free health services[10]. On the other hand, the private health clinics operate on a fee for service[9]. The Klang District has mainly a low-middle socioeconomic class population and chronic disease care is mainly provided from public health clinics[11]. Every public health clinic is led by Family Medicine Specialists, and are staffed by various healthcare providers: doctors, nurses, pharmacists, medical assistants and lab technicians. There were nine Family Medicine Specialists and 107 doctors at the time of study, all of whom were invited to participate. Written informed consent was obtained from every participant prior to carrying out the study.

Sampling method

The six clinics were purposively sampled to define characteristics that address the settings of low-middle income demographic. The characteristics of these clinics include government-subsidised and catered for a population which, majority were from low-middle income socio-economic groups. The size of population served by each clinic ranged from 82,000 to 156,672 people. Klang District is one of the most densely populated districts in Malaysia[12].

Data collection

We used a self-administered questionnaire to collect the data. The questionnaire was developed based on a literature review, training module on asthma for healthcare providers at the primary care level in Malaysia[13] and the views of an expert panel comprising a team of Family Medicine Specialists, respiratory physicians, and academicians in primary care medicine. Component 1 of the questionnaire includes questions on healthcare

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resources, clinic organisation as well as asthma services and treatment, which includes the availability of emergency care, training on asthma for healthcare providers, frequency of asthma clinical audits and availability of asthma medications. The number of resources and equipment available in designated areas in the clinic related to asthma was also collected. The questionnaire for Component 2 asked about the doctors' current practice on asthma management including number of years in service, number of patients with asthma seen in a month, tools used to diagnose asthma, use of spirometry, peak flow metre and asthma guidelines. The questionnaire was given to six Family Medicine Specialists, two respiratory physicians and five doctors to ensure its face and content validity and underwent a series of revisions where items were evaluated for clarity, easy comprehension, and formatting. The layout of the clinic areas was checked by the researchers prior to this study to better understand the availability of current resources and organisational support. This includes the layout of consultation rooms, treatment rooms (for nebulisation, immunisation, wound dressing), emergency room, pharmacy, laboratory, meeting room and room for continuous medical education (CME).

Data analysis

Statistical analysis was done using SPSS version 25.0. Descriptive statistics were used, where data were described using frequencies and percentages for categorical variables or means with standard deviation (SD) for continuous variables.

Ethical approval

We obtained ethical approval from the National Medical Research Ethics Committee, Ministry of Health, Malaysia (NMRR-18-2707-42719) and sponsor approval from the Academic and Clinical Central Office for Research and Development, University of Edinburgh United Kingdom (AC19040).

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

RESULTS

Component 1: healthcare resources and organisational support in asthma management

All data collected for Component 1 were captured objectively from patient registries, existing available clinic infrastructure and resources; and were reported by the Family Medicine Specialists from the six public health clinics. Table 1 summarises the provision and availability of healthcare resources and organisational support in asthma management. The average number of patients with asthma registered in each clinic ranged from 100 to 311 for adults and 30 to 100 for children and adolescents (less than 18 years old). However, two clinics reported they did not have registries for children or adolescents with asthma at the time of data collection. Most practices had dedicated asthma clinics which operated once a week or once a fortnight. These dedicated asthma clinics were run by trained healthcare personnel. An asthma appointment system was available in five clinics; however, only one had a system for tracing or recalling patients who defaulted follow-up. To enhance patients' adherence to treatment, four clinics had initiated an Asthma Medication Therapy Adherence Clinic (MTAC) run mainly by pharmacists. Oral corticosteroids for acute attacks and long-term controller medications, inhaled corticosteroids (ICS), and combination of inhaled corticosteroids and long-acting beta-agonist (ICS/LABA) were available but inadequate in quantities to meet the demand in the clinics. Leukotriene receptor antagonists (LTRA) were not available in any of the clinics. All clinics have a Critical Care Patient Escort and Retrieval Team (CPERT) system, which had been implemented to facilitate immediate referral of emergency cases to the tertiary centre when this system is activated. CPERT is a system unique to the district of Klang, Malaysia.

All six clinics have about similar layout. Each clinic has between 10 and 20 consultation rooms, one emergency room, one pharmacy and one consultation room for pharmacist, and one treatment room. Tables 2 and 3 summarise the total number of clinics with resources, educational materials and equipment for asthma and its availability in specified clinic rooms. Figures 1 and 2 demonstrate the availability of resources, education materials and equipment in the specified clinic rooms (consultation rooms, emergency rooms, pharmacies and treatment rooms). All clinics reported to have asthma care pathway and asthma treatment protocols, written asthma action plans, peak expiratory flow rate (PEFR) reference chart, children&rsqio;s growth chart, peak flow metres, pulse oximeters, nebulisers, oxygen supply and placebo inhalers. Although the resources, educational materials and equipment were provided in all clinics, the availability and placement of them varied. The clinics often had the materials and equipment they need, but not necessarily in the right places. Spacers were available in four clinics, and one clinic had handheld spirometry. Only three clinics had patient education leaflets for asthma.

Component 2: doctors' practice on asthma

A total of 107 doctors were invited to participate, however only 100 completed questionnaires were returned (94% response rate). Table 4 summarises the doctors' profile and how long they had been managing asthma. The average number of patients with asthma seen in a month was 19, most of whom they diagnosed by clinical assessment and peak flow metre measurements; with 65% of the doctors experienced carrying out a reversibility test with a peak flow metre. Only 18% used spirometry to diagnose asthma. The main reason for poor usage of spirometry was a lack of accessibility and familiarity. Peak flow rate was mainly assessed and documented during routine follow-up, and only about two-thirds of the doctors carried out peak flow assessment during unscheduled visits (potentially for an attack). History and examination (84%) and GINA assessment of asthma control (80%) were the main strategies for assessing asthma control. Most reported providing asthma action plans during consultations, though not to all the patients that they reviewed.

DISCUSSION

This study indicates there is room for improvement in the existing healthcare resources, organisational support and practices on asthma care. Four of the six clinics had dedicated asthma services run by teams of trained healthcare personnel. Five clinics had appointment systems for registered patients with asthma, however, only one clinic had a defaulter tracing system. All clinics had satisfactory provision of charts, tools, and equipment (e.g., peak flow metre, pulse oximeter, nebuliser machines) appropriate for asthma management, however, the availability in specified clinic rooms varied and appeared not to be readily available in important areas for use when needed during consultation or emergency care. Long-term controller medications for asthma for example ICS and combination ICS/LABA were available, though the latter were not adequately provided. To enhance compliance, four clinics had implemented a Medication Therapy Adherence Clinic (MTAC) programme for asthma run by pharmacists. Clinical assessment and peak flow readings appeared to be the main methods used to diagnose asthma, with more than half of the doctors surveyed reported conducting reversibility testing with peak flow metre. Only a minority had used spirometry, mainly due to lack of accessibility. Asthma action plans were still under-prescribed.

Table 1. Healthcare resources and organisational support in asthma management in the six public health clinics ($N = 6$).

1. Organisation of asthma services	
Total number of patients in each clinic (*N*)	(Adult/children & adolescents)
Clinic 1	240/not available
Clinic 2	288/not available
Clinic 3	300/100
Clinic 4	237/50
Clinic 5	100/30
Clinic 6	311/32
Availability of dedicated asthma clinic	4 clinics
Frequency of asthma clinic being held	Once a week or once every 2 weeks
Availability of asthma team	5 clinics
Comprises of Family Medicine Specialists (FMS), doctors, nurses, pharmacists and medical assistants (MA)	For each asthma team: -All 5 clinics have *FMS ($n = 1$ or 2), doctors ($n = 2$) and nurses ($n = 2$). -4 clinics have pharmacists ($n = 1$) -3 clinics have medical assistants ($n = 1$)
Received formal asthma training	All healthcare personnel in the asthma team
Availability of asthma appointment system	5 clinics
Availability of defaulter tracing or recall system	1 clinic
Availability of Medication Therapy Adherence Clinic (MTAC)[#] programme for asthma	4 clinics
Number of patients with asthma registered in past year, mean (range)	35 (1–110)
Proportion of patients with asthma (%) provided with asthma record book, mean (range)	57 (40–100)
Healthcare personnel who carried out assessment of asthma control	All doctors in all clinics Nurses and pharmacists in 3 clinics
2. Emergency care	
Availability of emergency medications	
Hydrocortisone, Prednisolone, Adrenaline, Salbutamol nebulised, Salbutamol/ipratropium nebulised	All clinics
Availability of ambulance services	All clinics
Availability of Critical Care Patient Escort and Retrieval Team (CPERT)[§] system	All clinics
3. Availability of long-term asthma treatment	
Availability of asthma medications	
1. Inhaled corticosteroids (ICS)	All clinics
Supply adequate?	Yes
2. Combination Long-Acting Beta-Agonist (LABA)/ Inhaled Corticosteroid (ICS) (Seretide and Symbicort)	All clinics
Supply adequate?	No
3. Theophylline	All clinics
Supply adequate?	Yes
4. Leukotriene receptor antagonist (LTRA)	Not available
4. Asthma training and audit	
Availability of asthma training (course/workshop)	All clinics
Frequency/year (range)	1–3 times/year
Availability of clinic audit for asthma care	All clinics
Frequency/year (range)	1–12 times/year
Availability of national-level Quality Assurance[+] for asthma	All clinics
Frequency/year (range)	1 time/year

[#]MTAC Medication Therapy Adherence Clinic—introduced in Malaysia in 2004 as a component of ambulatory care, with the aim to improve patient adherence to medication.
[§]CPERT Critical Care Patient Escort and Retrieval Team system to facilitate immediate referral of emergency cases to tertiary centre when this system is activated.
[+]Quality Assurance are measures taken by the specific practice to ensure the quality of care for patients with asthma are standardised throughout the practice, especially when involving many different doctors treating the patients.
*Three clinics have 2 FMSs and another two clinics have 1 FMS each.

Table 2. Total number of clinics with resources and educational materials for asthma and its availability in specified clinic rooms.

Resources and education materials	Asthma care pathway protocol	Asthma treatment protocol	Written AAP	PEFR reference chart	*Patient education leaflet	Growth chart for children
Availability in clinics ($N = 6$)	All clinics	All clinics	All clinics	All clinics	3 clinics	All clinics
Consultation room	√	√	√	√	√	√
Emergency room	√	√		√		
Pharmacy		√	√	√	√	
Treatment room	√	√		√		

AAP asthma action plan, *PEFR* peak expiratory flow rate.
*Patient education leaflet on asthma can be accessed from the Malaysia Ministry of Health website: http://www.myhealth.gov.my/en/asthma-2-2/.

Table 3. Total number of clinics with equipment for asthma and its availability in specified clinic rooms.

Equipment	Handheld spirometry	Peak flow metre	Pulse oximeter	Nebuliser	Oxygen	Placebo inhaler	Spacer
Availability in clinics $N = 6$	1 clinic	All clinics	All clinics	All clinics	All clinics	All clinics	4 clinics
Consultation room	√	√	√			√	
Emergency room		√	√	√	√		
Pharmacy		√				√	√
Treatment room		√	√	√	√		

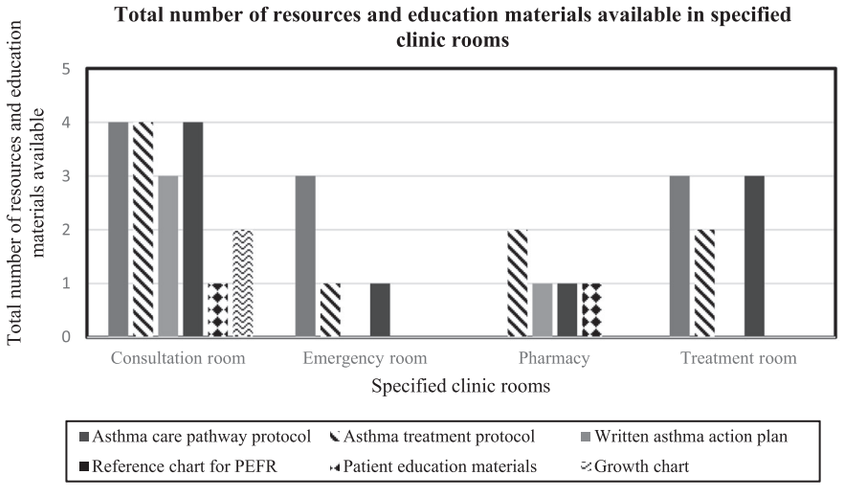

Fig. 1 The total number of resources and education materials available in specified clinic rooms (consultation room, emergency room, pharmacy and treatment room) in all clinics. PEFR peak expiratory flow rate.

Primary care settings are ideally placed to identify and manage patients with asthma. We found four of the six clinics provided dedicated asthma clinics, run by the Family Medicine Specialists, doctors, nurses and pharmacists who were trained in asthma care. Although, the outcome of dedicated asthma services has yet to be explored in the Malaysian primary care, a Cochrane review including studies from high-income countries like the United Kingdom and Australia reported promising results[14]. Asthma management provided by dedicated asthma clinics was associated with reduced emergency visits[15] and improved asthma control in Sweden and the United Kingdom[16]. Our study found only one clinic reported using a defaulter tracing system, despite evidences from earlier local studies in Malaysia and Korea that showed this system improved adherence on scheduled visits[17,18], and reduced unscheduled visits for acute exacerbations[18]. Implementing a defaulter tracing system in our primary care setting is important to facilitate attendances of follow-up clinics as only one-third of patients with asthma attended routine follow-up care[2,19]. Resources, educational material, and equipment for asthma for example, asthma care and treatment protocols, asthma action plans, PEFR reference charts and patient education leaflets are important to assist and facilitate healthcare providers in the clinic when managing asthma. We found some of these, including asthma action plans, were not available in important clinic areas such as the emergency rooms, consultation rooms, and pharmacies. A previous local qualitative study found the main reasons for this were budget constraints and lack of prioritisation[20]. Another local study documented adequate numbers of peak flow metres and PEFR reference charts provided in the clinic, however, there was no spacer or placebo inhalers available for teaching patients[21]. Readily available asthma protocols and charts in specific clinic

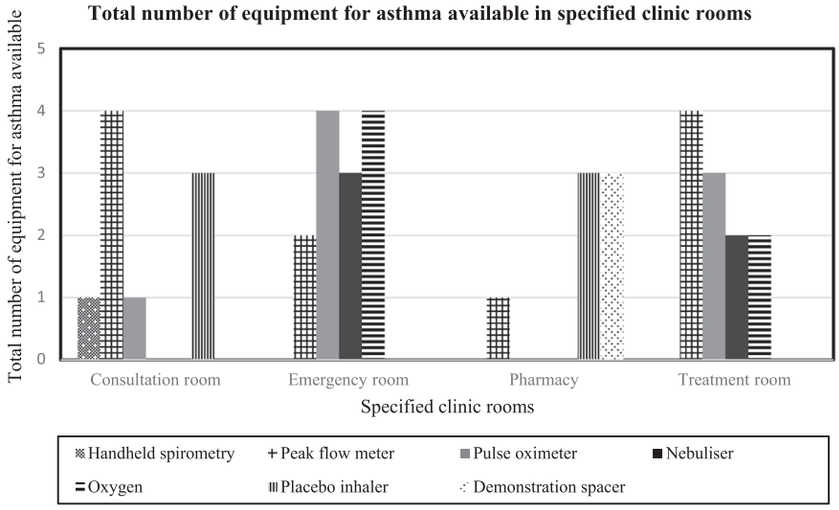

Fig. 2 The total number of equipment for asthma available in specified clinic rooms (consultation room, emergency room, pharmacy and treatment room) in all clinics.

areas (e.g., consultation or emergency rooms) would help healthcare providers on consultation and treatment decisions.

Asthma diagnosis remains a challenge, because of its variability in nature[22]. The GINA guidelines recommend the use of spirometry as a tool to assess lung function[23], but this assumes that spirometry is accessible, feasible and affordable in practice—which we found was not the case in any of our clinics. Studies conducted in Western countries found that accessibility was not the major issue, but rather underutilisation was due to lack of education and awareness of spirometer use and difficulties in interpreting the results[24–28]. Lack of confidence in use and interpretation was also reported a barrier in our study. One study reported the reason for underutilisation of spirometry testing was patient's unwillingness to undergo the test due to time constraint[29]. A primary care study echoed our findings that a clinical history supported by peak flow rate assessment of variability was the main strategy to arrive at a diagnosis of probable asthma[30]. This could be a pragmatic approach to diagnosing asthma in primary care in limited resource settings but further evidence on the accuracy of this approach is needed.

There was inadequate availability of long-term controller medications specifically ICS/LABA inhalers in our health clinics, which limit the supply to only a few of the patients with poorly controlled asthma, and under the provision of asthma action plans—a challenge shared with other countries[31–33]. The healthcare providers, especially those involved in dedicated asthma services, had attended asthma training, carried out regular asthma audits and performed quality assurance programmes, however, the effectiveness and impact of these activities on practice to improve asthma care has yet to be explored. Existing studies have documented inconsistencies of clinic practices and skill-based trainings[21,34,35].

This study highlights the gaps in resources, organisation, and practice, currently present in asthma care in our primary care setting. We suggest the following list of improvements in the delivery and organisation of asthma management:

i. **Increase accessibility to spirometry**. Correct asthma diagnosis is important for appropriate management; thus, it is important that spirometry and training in its use - is accessible in primary care settings. Currently spirometry is only provided at tertiary centres conducted by personnel certified by the Malaysian Thoracic Society[36], so peak flow rate measurement is the main tool used to diagnose asthma in our low-resource primary care settings.
ii. **Use of peak expiratory flow rate (PEFR) and reversibility test**. In the absence of spirometry due to resource constraints, PEFR and reversibility test can be used as a pragmatic tool to diagnose asthma. Several studies have suggested serial PEFR over a 2–4-week period to assess the amplitude of airway variability more than 20% to support the diagnosis of asthma, with the important caveat that lack of PEFR variability does not rule out asthma (because of natural variability in asthma control)[6,23,37]. Interpretation should always be supported by typical history of probable asthma[38–40]. If clinical history and PEFR are used as diagnostic tool, suggestions on the diagnostic algorithm and continuous medical education are needed on technique, interpretation, validity and limitations of use to support implementation[40]. Despite being available for many years, more evidence is needed to support the practical use of PEFR reversibility testing and serial PEFR in diagnosing asthma.
iii. **Implement a defaulter tracing system**. To optimise patients' adherence to follow-up asthma care, a defaulter tracing system should be in place to complement the existing appointment-based system. Several studies have shown regular asthma follow-up reduces the risk of exacerbation[17–19]. The use of telemedicine has a potential to improve follow-up care in asthma and asthma control[41].
iv. **Develop an 'asthma care kit'—a package to assist healthcare providers**. An asthma care kit that comprises of asthma education, assessment tools and treatment pathway protocols for both scheduled and unscheduled visits could potentially assist healthcare providers when reviewing patients. The 'asthma care kit' should be placed and easily reached by healthcare providers in all consultation and emergency rooms. There are promising results from implementation of an asthma care package in improving practice and patients outcomes[42,43].
v. **Upskill healthcare providers on asthma diagnosis, treatment and communication skills, particularly on asthma self-management**. This can be done through regular audits, training and educational programmes. The evidence-based practice which includes asthma self-management[44,45] needs to be encouraged, and long-term controller medications[23] should be made accessible to enhance doctors' practice in the treatment of poorly controlled asthma.

Table 4. Profile of doctors and their asthma practice ($N = 100$).

Profile	*n* (%)
Number of years working as a doctor, mean (SD)	10.1 (4.2)
Number of years working in primary care clinic, mean (SD)	6.0 (4.1)
Number of patients with asthma seen in a month, mean (range)	19 (1–80)
Methods used to diagnose asthma	
Clinical (History and physical examination)	96 (96.0)
Peak flow metre	84 (84.0)
Spirometry	18 (18.0)
Chest X-ray	5 (5.0)
Other (family history, oxygen saturation levels)	2 (2.0)
Number of doctors who had used spirometry to diagnose asthma:	18 (18.0)
If NOT, why	
Lack of accessibility	80 (80.0)
Lack of familiarity	20 (20.0)
Do not know how to interpret	10 (10.0)
Costly	4 (4.0)
Number of doctors who have carried out peak flow metre and reversibility test to diagnose asthma	65 (65.0)
Commonly peak flow expiratory rate (PEFR) measurement was carried out during	
Follow-up	96 (96.0)
Acute exacerbation	60 (60.0)
Walk-in	57 (57.0)
Number of doctors who reported prescribing asthma action plans	91 (91.0)
Mean (SD)	5.71 (3.46)
Main tool used for the assessment of asthma control	
History and examination	84 (84.0)
Global Initiative for Asthma (GINA) Guidelines	80 (80.0)
Peak Expiratory Flow Rate (PEFR)	77 (77.0)
Malaysian Clinical Practice Guidelines on Asthma	46 (46.0)
Asthma Control Test (ACT)	35 (35.0)
Asthma Control Questionnaires (ACQ)	11 (11.0)
Main asthma management guidelines used	
Global Initiative for Asthma (GINA) Guidelines	96 (96.0)
Malaysian Clinical Practice Guidelines on Asthma	63 (63.0)
National Institute for Health and Care Excellence (NICE) Guideline	8 (8.0)

The strength of this study was the response rate of 94% was excellent. Nevertheless, several limitations were identified. Reasons behind the identified gaps in care were not explored; this includes an unavailable defaulter tracing system, inadequate provision of ICS/LABA in clinics, and variation in the number of resources, equipment and materials for asthma in the specified clinic rooms. This could be explored further qualitatively. In addition, only Family Medicine Specialists and the doctors were invited to participate in the survey because they were the most involved in asthma care at the time of data collection. The Family Medicine Specialists led and organised asthma care in the clinic. Diagnosing asthma, assessing asthma control, prescribing, and counselling were mainly carried out by the doctors.

It would have added value if other healthcare providers (e.g., nurses and pharmacists) completed the survey. In addition, it was a self-reported questionnaire; doctors' actual practice in patients' clinical records was not evaluated to observe the match between reported and actual practice.

This study has demonstrated opportunities to further improve the provision of healthcare resources, organisational support, educational materials, and equipment for asthma in our primary care setting. Spirometry was rarely utilised in asthma diagnosis as compared to the use of peak flow measurements with reversibility testing, suggesting that this is a practical alternative to spirometry in a low-resource setting. Reinforcing education on asthma action plan deserves to be addressed to ensure asthma care is optimised.

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon request.

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AUTHOR CONTRIBUTIONS

All authors have made contributions to the work in conceptualisation, conception, design of work and analysis. NH and JP wrote the original draft, and all authors reviewed and edited critically for intellectual content. All authors have read and approved the final version of the manuscript. The views expressed in this manuscript are those of the author(s) and not necessarily those of the NIHR or the UK Department of Health and Social Care.

COMPETING INTERESTS

The authors E.M.K., P.Y.L., A.T.C. and H.P. declare no competing non-financial interests but the following competing financial interests: E.M.K., P.Y.L., A.T.C. and H.P. declare grants from the National Institute for Health Research (NIHR) Global Health Research Unit on Respiratory Health (RESPIRE). E.M.K. reports grants from Seqirus UK; consulting fees from AstraZeneca and GlaxoSmithKline; and is the board director of the International Primary Care Respiratory Group. E.M.K. and H.P. are associate editors for *npj Primary Care Respiratory Medicine*. E.M.K. and H.P. were not involved in the journal's review of, or decisions related to, this manuscript. The remaining authors declare no competing interests.

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Asthma control among treated US asthma patients in Practice Fusion's electronic medical record research database

Jonathan Davitte[1], Bailey DeBarmore[2], David Hinds[2], Shiyuan Zhang[3]✉, Jessica Chao[1] and Leah Sansbury[2]

This study investigated burden of 'not well-controlled' asthma, overall and by Global Initiative for Asthma (GINA) Step, among treated asthma patients in Practice Fusion's research database. Asthma control (Asthma Control Test [ACT]) was stratified by GINA Step; prevalence ratios were estimated using Poisson regression with robust variance controlled for confounders. ACT scores ≤19 reflect not well-controlled; >19 reflect 'well-controlled' asthma. Of 15,579 patients, 30% had not well-controlled asthma at index date. The proportion of patients with not well-controlled asthma increased from GINA Step 1 (29%) to Step 5 (45%). Compared with Step 1, the proportion of patients with not well-controlled asthma was 0.87-times lower in Step 2, 1.10-times greater in Step 4, and 1.37-times greater in Step 5. Results suggest that despite available treatments, patients remain symptomatic across GINA Steps in real-world primary care and specialist outpatient practices, with incremental disease burden and unmet medical need in these populations.

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INTRODUCTION

Asthma is a chronic, heterogenous disease, usually characterized by chronic airway inflammation and defined by a history of respiratory symptoms including wheeze, shortness of breath, chest tightness and cough that varies both over time and in intensity together with variable expiratory airflow limitation[1]. Asthma affects 1–18% of the population across different countries[1]. In the United States (US) alone, there were an estimated 25.1 million individuals living with asthma in 2019[2]. Asthma control is defined as the degree to which asthma manifestations, such as symptoms, reliever use, lung function and exacerbations, are reduced or removed by treatment[3], and has a major impact on patient outcomes; poor control of asthma symptoms substantially impairs health-related quality of life and is strongly associated with an increased risk of future asthma exacerbations[4–8]. The contribution of asthma severity to patient outcomes is also important to consider, as more severe forms of the disease are associated with greater symptom burden and higher asthma-related healthcare costs[9–11]. Asthma severity is determined by the intensity of treatment required to maintain good control, with more severe and difficult-to-treat asthma requiring higher dosages or supplemental treatments[3].

The Global Initiative for Asthma (GINA) report recommends that asthma symptom control should be assessed at every opportunity, including during routine prescribing or dispensing, via direct questioning regarding symptoms and instruments designed to assess asthma control[1]. While several patient-reported instruments are available to assess asthma control, recording and integration into electronic health records (EHR) and other real-world data sources as part of routine clinical practice is limited. Consequently, while these real-world data sources contain rich data for recording asthma diagnoses and describing asthma treatment (e.g., prescriptions, claims), they have limited ability to describe asthma symptom control based on validated instruments.

In 2015, the Practice Fusion Electronic Medical Record (EMR) database integrated the Asthma Control Test (ACT) into their platform. The ACT is a patient-reported measure commonly used to distinguish different levels of symptom control by evaluating the frequency of shortness of breath and general asthma symptoms, use of rescue medications, the effect of asthma on daily functioning, and overall self-assessment of asthma control[12]. Practice Fusion, a free EMR platform, generates a notification for clinicians to consider administering the ACT or the childhood ACT (for children aged 4–11 years), whenever a patient with asthma visits the office.

The GINA report recommends that once asthma treatment has been started, ongoing decisions should be based on regular patient assessments and adjustment of treatment[1]. The asthma treatment paradigm involves five 'treatment steps', where asthma treatment is adjusted based on changes in asthma control status. The Steps outlined in the GINA 2019 report correspond to asthma severity: mild asthma is controlled with Step 1 or 2 treatment (as-needed controller medication alone or with low-intensity maintenance controller treatment); moderate asthma is controlled with Step 3 treatment (e.g., low-dose inhaled corticosteroids/long-acting b2 agonist [ICS/LABA]); and severe asthma requires Step 4 or 5 treatment (high-dose ICS/LABA or add-on treatments) to prevent it from becoming uncontrolled or remains uncontrolled despite this treatment[13,14]. Clinicians may recommend stepping up or stepping down asthma treatment to improve asthma control.

This study investigated the burden of not well-controlled asthma both overall, and by GINA treatment step (GINA Step), among the treated asthma patient population in Practice Fusion's research database. While many real-world data sources allow for the investigation of asthma treatment status and patterns, along with indicators of asthma control, the absence of data from patient-reported tools in secondary sources inhibits the ability of researchers to understand the burden of not well-controlled asthma outside of clinical trials or other research settings. The Practice Fusion research database, with the integrated ACT tool, is uniquely positioned to describe asthma control among the

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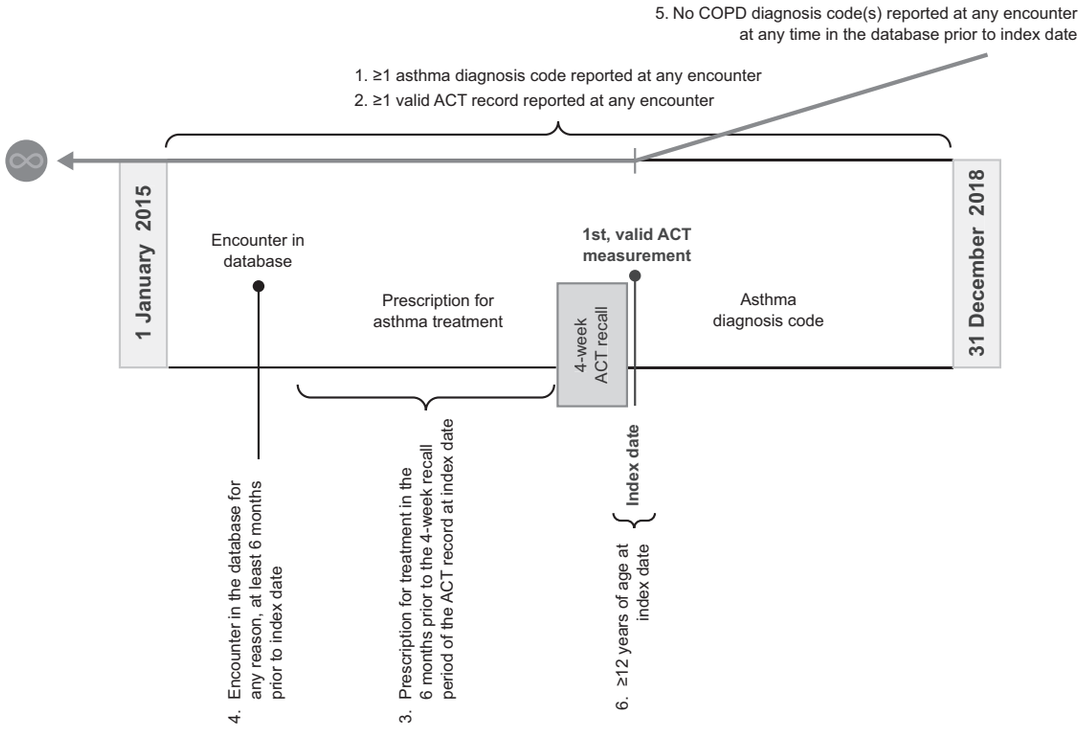

Fig. 1 Study design. ACT asthma control test; Chronic obstructive pulmonary disease.

treated asthma population as it exists in real-world primary care and specialist outpatient practices.

METHODS

Study population

A retrospective cohort was established which included patients with asthma and a valid ACT measurement in Practice Fusion's EMR database between January 1, 2015 and December 31, 2018, and with at least 1 prescription for any asthma treatment in the 6 months prior to the 4-week recall period of their first valid ACT measurement. The date of a patient's first valid ACT measurement was defined as their index date. Patients were required to have activity in the database, defined as an encounter in the database for any reason, at least 6 months (182 days) prior to their index date. In addition, patients were excluded from our sample if they had ≥1 chronic obstructive pulmonary disease diagnosis code(s) reported at any time on or before their index date or had a missing value for their calendar year of birth (Fig. 1).

Data source

Practice Fusion is a cloud-based connected health platform used in 30,000 healthcare practices with 8% market share among small practices (1–3 physicians) in the US, is linked with 90% of US pharmacies, and 600 laboratory and imaging entities. Practices were included in Practice Fusion's research database if they met any of the following criteria: over 13,000 chart pulls; 1 or more providers with a verified National Provider Identifier and over 500 chart pulls; sent 500 or more electronic prescriptions; sent 500 or more laboratory orders. Practices were excluded if they were used by Practice Fusion for testing and production purposes, did not have at least one Doctor of Medicine, or were located outside the US. Practice Fusion's research database contained patient-level data on demographics, office visits, insurance, allergies, vitals, medications, laboratory tests, diagnoses, prescriptions, and immunizations. As of December 2018, the cut of Practice Fusion's research database contained data for 1.9 million asthma patients with ≥1 ICD-9 493.xx, ICD-10 J45.xx, or SNOMED-CT CTV3 H33xx diagnosis codes between 2007 and 2018 with patients across all 50 US states.

The database is certified as statistically de-identified through the removal of all personally identifiable indicators, transformation of dates, generalization of certain demographic and geographic information, standardization of free text and other sensitive fields, and substitution of patient- and provider-related unique identifiers with random values.

Asthma control

The ACT is comprised of five questions, each item response is captured on a 5-point scale (where 1 is the worst scenario and 5 is the best) utilizing a 4-week recall period. ACT scores range from 5 (poor control of asthma) to 25 (complete control of asthma) with higher scores reflecting greater asthma control. ACT scores ≤19 reflect not well-controlled asthma while ACT scores >19 reflect well-controlled asthma[15].

Beginning in 2015, Practice Fusion implemented a clinical decision support program that notified providers that an ACT should be conducted when a patient with asthma missing symptom assessments visited them. While the notification indicated that an ACT should be completed, the system did not require clinicians to complete and/or record the ACT results.

We defined a valid ACT as: (1) having complete responses for all 5 questions; (2) not occurring on the same date as another ACT measurement for the same patient; and (3) not occurring within 28 days of another ACT measurement for the same patient. Scores that reflect asthma control as measured by the ACT cannot be calculated if any of the 5 questions are missing responses. The rationale behind this 28-day time gap is that the ACT reflects a 4-week recall period; if two ACT scores are measured on the same day or within 28 days of each other, it is impossible to determine which of these indicate the correct measurement of asthma control.

GINA step

GINA Step was assessed based on the medications prescribed during the 6-month period prior to the 4-week recall period of patients' ACT record at index date. Asthma treatment was defined as one of the following medications: short-acting β_2-agonists (SABA), short-acting muscarinic antagonist (SAMA), inhaled corticosteroids (ICS), ICS and long-acting β_2-agonist (ICS/LABA) combination products, leukotriene receptor antagonist, cromolyn or nedocromil (mast cell stabilizers), methylxanthines, biologics (e.g., mepolizumab) or long-acting muscarinic antagonist. Further details on GINA Step definition and asthma treatments are in Supplementary Table 1.

Determination of a patient's GINA Step required calculation of ICS and ICS/LABA daily doses. The Practice Fusion prescription data includes fields that were generated using MedEx, a natural language processing system which extracts medication information from clinical notes[16]. There are three MedEx-derived fields that were used for calculation of ICS daily dose: (1) frequency *(e.g., once per day)*; (2) dose amount (*e.g., '2' in '2 puffs'*); (3) dose unit (*'puff' in '2 puffs'*). For missing values of frequency, dose, or dose amount, we imputed values from the mode across each National Drug Code. We converted all ICS strength to micrograms (mcg) prior to calculating ICS daily dose[17]. ICS daily dose was calculated as: *(Frequency)*(Dose amount)*(Strength)*. Finally, the ICS and ICS/LABA dosage levels required for GINA Step calculation were defined for each medication based on generic names or ingredients (Supplementary Table 2).

ICS/LABA includes fixed-dose ICS/LABA combination medications and 'open' ICS/LABA combinations. For patients that had individual ICS and LABA prescriptions, we considered them as 'open' ICS/LABA combinations only if the ICS medication and LABA medication were prescribed within 30 days of each other. Patients with separate ICS and LABA prescriptions more than 30 days apart were considered as 'ICS only' in the GINA Step calculation. For patients that had multiple ICS or ICS/LABA prescriptions in the eligible period, we used only the prescription(s) that were closest to the patient's index date for calculation of the ICS daily dose.

GINA steps were defined according to GINA asthma treatment guidelines in 2018[17]. The GINA 2019 treatment guidelines include the addition of as-needed low-dose ICS-formoterol for Step 1[13]. Given that this additional criteria for Step 1 did not align with our observation period, we chose to define GINA Step according to the guidelines clinicians would have followed at the time they prescribed asthma medications in our study. We assumed that any oral corticosteroid (OCS) use was not used continuously (e.g., supply ≤28 days) by the patient and thus had no impact on GINA Steps. This decision was made given the difficulty in calculating a consistent day supply for OCS from the Practice Fusion prescription data. Treatment with SABA, SABA-SAMA, or SAMA was classified simply as SABA. Treatment with SABA only was defined as GINA Step 1. However, SABA use was allowed in all other steps. All individuals that were missing key information required for the GINA Step determination or had combinations of prescriptions that did not clearly meet definitions for a GINA Step were classified as 'Undefined'.

Covariates

Age in years was calculated as the difference between the calendar year of a patient's index date and their birth year. Ethnicity was defined as 'Hispanic', 'Non-Hispanic' or 'Missing'. Race was defined as 'White', 'Black/African American', 'Other' and 'Unknown'. 'Unknown' race was assigned to individuals that had conflicting responses for race at any time in the database (e.g., patients may have multiple race information) or did not have any documentation of race in the Practice Fusion database. 'Current' smoking status was assigned to patients with a status of 'current smoker' on the smoking status record closest to their index date. 'Former' was assigned to patients with smoking status of 'former smoker' at any time on or before their index date. 'Non-smoker' was assigned to patients with only records of 'non-smoker' at any time in the database on or prior to their index date. Finally, we used the value for body mass index (BMI) in kg/m^2 that was recorded on the individual's index date or a prior record closest (e.g., least number of days) to the index date. Visit type was categorized according to the specialty of the provider with whom the patient had an appointment for the encounter on their index date: 'Primary Care' includes 'Internal Medicine', 'General Medicine', and 'Family Medicine'; 'Specialist' includes 'Allergy and Immunology', 'Pulmonary Disease', and 'Emergency Medicine'; 'Other' includes all other specialties.

Statistical analysis

Descriptive frequencies both overall and by patient asthma control status at index date were calculated for each GINA Step. We used Poisson regression with robust variance to directly estimate the prevalence ratio (PR) and 95% confidence intervals (95% CI) of not well-controlled asthma by patient GINA Step at index date, adjusting for age, race, Hispanic ethnicity, smoking status, BMI, and the visit type at index date. Given that not well-controlled asthma was quite common in our study population (e.g., >10%), odds ratios derived from logistic regression would violate the rare disease assumption and consequently would overestimate the strength of associations and not approximate the relative risk[18]. However, Poisson regression models with robust variance can directly estimate the PR and are a suitable alternative to logistic regression modeling in cross-sectional studies with a dichotomous outcome[19]. The primary exposure of interest was GINA Step at index date with Step 1 as the reference group. The dependent variable (outcome) was not well-controlled asthma at index date, defined as an ACT score ≤19. We used a Directed Acyclic Graph to identify covariates for confounding control in the regression model. The final model included age (in years), BMI, race, Hispanic ethnicity, smoking status, and type of visit at index date.

Ethics

The data used in this study are data collected from routine activity as part of patients' interactions with the healthcare system through their provider's medical records software. The original data collection is for administration and healthcare delivery purposes but is aggregated and deanonymized for research purposes. The analysis used fully deidentified retrospective data, and as such, this is not classified as research involving human participants as defined by 45 CFR 46.102(f) under the US Department of Health and Human Services Policy for Protection of Human Subjects (https://www.hhs.gov/ohrp/regulations-and-policy/regulations/2018-req-preamble/index.html). Therefore, institutional review board approval and informed consent were not required.

Reporting summary

Further information on research design is available in the Nature Research Reporting Summary linked to this article.

RESULTS

Overall baseline characteristics

Overall baseline characteristics are shown in Table 1. We identified 15,579 treated patients with asthma for our study sample after applying all inclusion and exclusion criteria (Fig. 2). Overall, the sample had a mean age of 44 years (standard deviation = 22) and was predominantly female (64%, $n = 9995$), non-Hispanic (80%, $n = 12{,}489$), and white (46%, $n = 7153$) (Table 1). The majority of the sample received their index ACT record at a primary care visit (55%, $n = 8527$) with 22% ($n = 3352$) receiving their index ACT at a specialist visit and 22% ($n = 3485$) at a non-primary care/non-specialist visit.

Table 1. Asthma control status and patient characteristics by GINA Step among the treated asthma patient population, Practice Fusion EMR, 2015–2018 ($N = 15,579$).

Characteristics	GINA step[a]						Overall ($N = 15,579$)
	Step 1 ($N = 5374$)	Step 2 ($N = 3751$)	Step 3 ($N = 2187$)	Step 4 ($N = 3909$)	Step 5 ($N = 165$)	Undefined ($N = 193$)	
Asthma control[b], *n* (%)							
Not well-controlled	1572 (29.3)	940 (25.1)	617 (28.2)	1331 (34.0)	74 (44.8)	63 (32.6)	4597 (29.5)
Well-controlled	3802 (70.7)	2811 (74.9)	1570 (71.8)	2578 (66.0)	91 (55.2)	130 (67.4)	10982 (70.5)
Age in years							
Mean (SD)	39.4 (21.8)	44.1 (22.7)	43.9 (22.7)	49.3 (20.6)	55.9 (16.6)	54.9 (19.5)	44.0 (22.2)
Range	12.0–88.0	12.0–88.0	12.0–88.0	12.0–88.0	12.0–87.0	12.0–88.0	12.0–88.0
Sex, male, *n* (%)	1996 (37.1)	1310 (34.9)	787 (36.0)	1359 (34.8)	59 (35.8)	73 (37.8)	5584 (35.8)
Hispanic ethnicity, Yes, *n* (%)	1150 (21.4)	680 (18.1)	426 (19.5)	786 (20.1)	15 (9.1)	33 (17.1)	3090 (19.8)
Race[c], *n* (%)							
White	2362 (44.0)	1864 (49.7)	946 (43.3)	1826 (46.7)	64 (38.8)	91 (47.2)	7153 (45.9)
African American	946 (17.6)	557 (14.8)	402 (18.4)	647 (16.6)	30 (18.2)	29 (15.0)	2611 (16.8)
Other	424 (7.9)	280 (7.5)	201 (9.2)	321 (8.2)	6 (3.6)	21 (10.9)	1253 (8.0)
Unknown	1642 (30.6)	1050 (28.0)	638 (29.2)	1115 (28.5)	65 (39.4)	52 (26.9)	4562 (29.3)
Smoking status[d], *n* (%)							
Non-smoker	3467 (64.5)	2677 (71.4)	1482 (67.8)	2589 (66.2)	90 (54.5)	114 (59.1)	10419 (66.9)
Former smoker	628 (11.7)	452 (12.1)	307 (14.0)	602 (15.4)	34 (20.6)	39 (20.2)	2062 (13.2)
Current smoker	660 (12.3)	244 (6.5)	172 (7.9)	373 (9.5)	19 (11.5)	26 (13.5)	1494 (9.6)
Unknown	619 (11.5)	378 (10.1)	226 (10.3)	345 (8.8)	22 (13.3)	14 (7.3)	1604 (10.3)
Body mass index[e], kg/m^2							
Mean (SD)	31.1 (8.4)	31.1 (8.1)	31.1 (8.3)	31.9 (8.3)	33.2 (9.0)	31.0 (8.8)	31.3 (8.3)
Range	13.7–68.3	15.3–66.4	14.3–64.5	14.6–70.4	16.5–60.5	15.7–60.5	13.7–70.4
Body mass index category, *n* (%)							
Underweight	100 (1.9)	70 (1.9)	33 (1.5)	55 (1.4)	1 (0.6)	7 (3.6)	266 (1.7)
Normal	964 (17.9)	662 (17.6)	427 (19.5)	651 (16.7)	21 (12.7)	39 (20.2)	2764 (17.7)
Overweight	1179 (21.9)	853 (22.7)	474 (21.7)	938 (24.0)	44 (26.7)	49 (25.4)	3537 (22.7)
Obese	2116 (39.4)	1511 (40.3)	894 (40.9)	1921 (49.1)	90 (54.5)	85 (44.0)	6617 (42.5)
Unknown	1015 (18.9)	655 (17.5)	359 (16.4)	344 (8.8)	9 (5.5)	13 (6.7)	2395 (15.4)
Visit type, *n* (%)							
Primary care	3061 (57.0)	2064 (55.0)	1058 (48.4)	2158 (55.2)	65 (39.4)	121 (62.7)	8527 (54.7)
Specialist	570 (10.6)	820 (21.9)	585 (26.7)	1234 (31.6)	92 (55.8)	51 (26.4)	3352 (21.5)
Other	1664 (31.0)	819 (21.8)	514 (23.5)	466 (11.9)	6 (3.6)	16 (8.3)	3485 (22.4)
Unknown/missing	79 (1.5)	48 (1.3)	30 (1.4)	51 (1.3)	2 (1.2)	5 (2.6)	215 (1.4)

[a]GINA Step defined using prescriptions for asthma treatment in the 6 months prior to the 4-week recall period of patient's index date ACT record.
[b]Asthma control defined by ACT scores: 'Not well-controlled' ≤19 and 'Well-controlled' >19.
[c]'Unknown' race assigned to patients that have (1) conflicting responses for race and/or (2) no entries for race recorded in the system.
[d]'Current' smoking status assigned to patients with a status of 'current smoker' on the date closest to index date. 'Former' assigned to patients with smoking status of 'former smoker' at any time before their index date. 'Non-smoker' assigned to patients with only records of 'non-smoker' at any time in the database prior to their index date.
[e]Body mass index measurement recorded on the same date or the date closest to their index date.
ACT asthma control test, *EMR* electronic medical record, *GINA* Global Initiative for Asthma, *SD* standard deviation.

Baseline demographics and characteristics by GINA step

Individuals in GINA Step 1 were younger than the other GINA Step groups: mean 39.4 years for Step 1 compared with 44–56 years for Steps 2–5 and 'Undefined'. Patients in the Step 5 GINA group were the oldest (mean 56 years). The sex composition was similar across all GINA Steps with males comprising 35 to 38% of each GINA Step group (Table 1).

Approximately 20% of patients in GINA Steps 1–4 and Undefined groups were of Hispanic Ethnicity. By comparison, GINA Step 5 had substantially fewer individuals of Hispanic Ethnicity (9.1%, $n = 15$). The racial composition for white and African Americans across GINA Step groups (1–5) was relatively similar with 39–50% and 15–18%, respectively. While proportion of patients self-identifying as 'Other' and 'Unknown' race were similar for GINA Steps 1–4 and Undefined groups, GINA Step 5 had a much smaller proportion of patients identifying as 'Other' race and a greater proportion of those with 'Unknown' race.

While GINA Steps 1–4 groups had similar proportions of non-smokers (65–71%) and former smokers (12–15%), Step 5 and 'Undefined' groups had fewer non-smokers (55%, $n = 90$ and 59%, $n = 114$, respectively) and more former smokers (21%, $n = 34$ and 20%, $n = 39$, respectively). The greatest proportion of current smokers was observed in the 'Undefined' GINA Step group (14%,

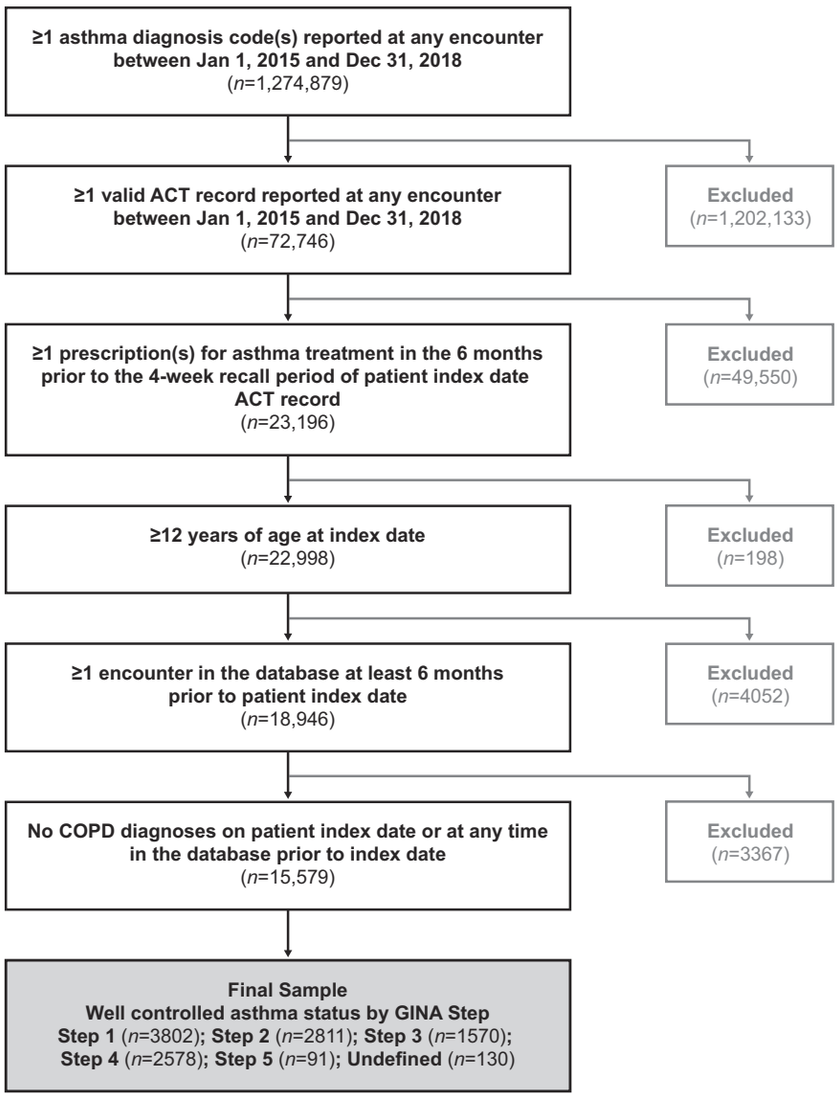

Fig. 2 Construction of study sample. Inclusion and exclusion criteria applied to construct the final study sample. ACT asthma control test, COPD chronic obstructive pulmonary disease, GINA Global Initiative for Asthma.

$n = 26$) followed by Step 1 (12%, $n = 660$), Step 5 (12%, $n = 19$), Step 4 (10%, $n = 373$), Step 3 (8%, $n = 172$), and Step 2 (7%, $n = 244$).

The percentage of individuals with 'Obese' BMI increased from GINA Step 1–5 with 39% ($n = 2116$) in Step 1, 40% ($n = 1511$) in Step 2, 41% ($n = 894$) in Step 3, 49% ($n = 1921$) in Step 4, and 55% ($n = 90$) in Step 5.

Similar proportions of ACT records at index date were recorded in primary care visits for GINA Steps 1–4 (48%–57.0%). However, relatively few individuals in GINA Step 1 received their index date ACT at a specialist visit (1%, $n = 570$) compared with 56% ($n = 92$) for Step 5, 32% ($n = 1234$) for Step 4, 27% ($n = 585$) for Step 3, and 22% ($n = 820$) for Step 2.

Asthma control overall and by GINA step

At index date, 30% ($n = 4597$) of individuals had not well-controlled asthma compared with 71% ($n = 10{,}982$) with well-controlled asthma (Table 1). With respect to GINA Step, 35% ($n = 5374$) of the overall population were classified in Step 1; 24% ($n = 3751$) in Step 2; 14% ($n = 2187$) in Step 3; 25% ($n = 3909$) in Step 4; 1% ($n = 165$) in Step 5; and 1% ($n = 193$) were 'Undefined' GINA Step (Table 2). Distribution by GINA Step was similar for individuals with not well-controlled asthma compared with individuals with well-controlled asthma for Step 1 (34%, $n = 1572$ vs. 35%, $n = 3802$), Step 3 (13%, $n = 617$ vs. 14%, $n = 1570$), and 'Undefined' (1%, $n = 63$ vs. 1%, $n = 130$). However, fewer individuals with not well-controlled asthma were classified in GINA Step 2 compared with individuals with well-controlled asthma: 20% ($n = 940$) and 26% ($n = 2811$), respectively. By comparison, a larger proportion of individuals with not well-controlled asthma were classified as GINA Step 4 and Step 5 compared with individuals with well-controlled asthma; 29% ($n = 1331$) of individuals with not well-controlled asthma were in Step 4 compared with 23% ($n = 2578$) with well-controlled asthma, and in Step 5 the proportions were 2% ($n = 74$) and 1% ($n = 91$), respectively (Table 2).

Across all GINA Steps more than a quarter of individuals were classified as having not well-controlled asthma (Table 1). Figure 3 illustrates the absolute numbers and percentages of individuals with well-controlled and not well-controlled asthma at their index date by GINA Step. The largest proportion of individuals with not well-controlled asthma was within GINA Step 5 (45%, $n = 74$);

Table 2. GINA Step, patient characteristics and provider characteristics by asthma control status among the treated asthma patient population, Practice Fusion EMR, 2015–2018 ($N = 15,579$).

	Asthma control status[a]		Overall ($N = 15,579$)
	Well-controlled ($N = 10,982$)	Not well-controlled ($N = 4597$)	
GINA step[b]			
Step 1	3802 (34.6%)	1572 (34.2%)	5374 (34.5%)
Step 2	2811 (25.6%)	940 (20.4%)	3751 (24.1%)
Step 3	1570 (14.3%)	617 (13.4%)	2187 (14.0%)
Step 4	2578 (23.5%)	1331 (29.0%)	3909 (25.1%)
Step 5	91 (0.8%)	74 (1.6%)	165 (1.1%)
Undefined	130 (1.2%)	63 (1.4%)	193 (1.2%)
Age			
Mean (SD)	43.1 (22.7)	46.3 (20.8)	44.0 (22.2)
Range	12.0–88.0	12.0–88.0	12.0–88.0
Sex, male, *n* (%)	4099 (37.3)	1485 (32.3)	5584 (35.8)
Hispanic ethnicity, Yes, *n* (%)	2185 (19.9)	905 (19.7)	3090 (19.8)
Race[c], *n* (%)			
White	5154 (46.9)	1999 (43.5)	7153 (45.9)
African American	1784 (16.2)	827 (18.0)	2611 (16.8)
Other	927 (8.4)	326 (7.1)	1253 (8.0)
Unknown	3117 (28.4)	1445 (31.4)	4562 (29.3)
Smoking status[d], *n* (%)			
Non-smoker	7547 (68.7)	2872 (62.5)	10,419 (66.9)
Former smoker	1389 (12.6)	673 (14.6)	2062 (13.2)
Current smoker	895 (8.1)	599 (13.0)	1494 (9.6)
Unknown	1151 (10.5)	453 (9.9)	1604 (10.3)
Body mass index[e], kg/m^2			
Mean (SD)	30.9 (8.1)	32.2 (8.7)	31.3 (8.3)
Range	13.7–68.3	14.6–70.4	13.7–70.4
Body mass index category, *n* (%)			
Underweight	187 (1.7)	79 (1.7)	266 (1.7)
Normal	1993 (18.1)	771 (16.8)	2764 (17.7)
Overweight	2539 (23.1)	998 (21.7)	3537 (22.7)
Obese	4385 (39.9)	2232 (48.6)	6617 (42.5)
Unknown	1878 (17.1)	517 (11.2)	2395 (15.4)
Visit type, *n* (%)			
Primary care	5795 (52.8)	2732 (59.4)	8527 (54.7)
Specialist	2358 (21.5)	994 (21.6)	3352 (21.5)
Other	2679 (24.4)	806 (17.5)	3485 (22.4)
Unknown/missing	150 (1.4)	65 (1.4)	215 (1.4)
Practice census region, *n* (%)			
Midwest	1856 (16.9)	819 (17.8)	2675 (17.2)
Northeast	2279 (20.8)	921 (20.0)	3200 (20.5)
South	4607 (42.0)	1831 (39.8)	6438 (41.3)
West	1697 (15.5)	763 (16.6)	2460 (15.8)
Unknown	543 (4.9)	263 (5.7)	806 (5.2)

ACT asthma control test, *EMR* electronic medical record, *GINA* Global Initiative for Asthma, *SD* standard deviation.
[a]Asthma control defined by ACT scores: 'Not well-controlled' ≤19 and 'Well-controlled' >19.
[b]GINA Step defined using prescriptions for asthma treatment in the 6 months prior to the 4-week recall period of patient's index date ACT record.
[c]'Unknown' race assigned to patients that have (1) conflicting responses for race and/or (2) no entries for race recorded in the system.
[d]'Current' smoking status assigned to patients with a status of 'current smoker' on the date closest to index date. 'Former' assigned to patients with smoking status of 'former smoker' at any time before their index date. 'Non-smoker' assigned to patients with only records of 'non-smoker' at any time in the database prior to their index date.
[e]Body mass index measurement recorded on the same date or the date closest to their index date.

although it should be noted that relatively few individuals were classified in GINA Step 5 ($n = 165$) compared with the other steps. Among GINA Steps 1–4 (which had similarly large numbers of individuals), the largest burden of not well-controlled asthma was present in GINA Step 4 (34%, $n = 1331$) followed by Step 1 (29%, $n = 1572$), Step 3 (28%, $n = 617$), and Step 2 (25%, $n = 940$). Additional information on asthma control distribution by patient and provider characteristics can be found in Table 2.

Association between GINA step and asthma control at index date

Compared with patients in Step 1, the proportion of patients with not well-controlled asthma was 0.87 times lower among patients in Step 2 (PR: 0.87, 95% CI: 0.79–0.94), 1.10 times greater among patients in Step 4 (PR: 1.10, 95% CI: 1.03–1.16), and 1.37 times greater among patients in Step 5 (PR: 1.37, 95% CI: 1.19–1.55), after adjusting for age, race, Hispanic ethnicity, smoking status, BMI, and visit type at index date (Fig. 4). We did not observe significant differences in not well-controlled asthma among patients in Step 3 compared with Step 1 in our fully adjusted model.

DISCUSSION

Results from this sample of 15,579 treated patients with asthma in the US showed that despite a variety of available treatments, patients with asthma remain symptomatic across GINA Steps in real-world primary care and specialist outpatient practices. At index date, nearly one-third of our sample had not well-controlled asthma despite receiving prescriptions for asthma treatment in the 6 months prior to the 4-week recall period of their ACT record. The proportion of patients with not well-controlled asthma in our sample was lower than in previous studies under more controlled study design[20,21]. This may indicate a potential bias in patients that were administered the ACT. We observed an increasing proportion of individuals with not well-controlled asthma from GINA Step 1 to GINA Step 5 in our descriptive analysis. However, when comparing GINA Steps, our modeling results only showed significant differences in the proportion of patients with not well-controlled asthma between Steps 2, 4, and 5 compared with Step 1 after full adjustment (not Step 3). We observed significantly better asthma control in GINA Step 2 compared with GINA Step 1; while we observed significantly worse asthma symptom control in GINA Steps 4 and 5 compared with GINA Step 1. The finding that asthma control was significantly better in GINA Step 2 compared with Step 1 may also suggest that patients in the Step 1 group are misclassified and undertreated, and therefore should be assigned to a higher GINA Step.

The significantly better asthma control among patients in GINA Step 2 compared with GINA Step 1 may be attributed to the addition of a regular controller medication in addition to a reliever medication in Step 2 compared with only a reliever for Step 1. As-needed SABA with no controller was the recommendation for Step 1 in the GINA 2018 guidelines which were used during the observation period for this study[17]. However, in a major change from the 2018 recommendations, the GINA 2019 guidelines no longer recommend SABA-only treatment (without ICS) and instead recommend as-needed low-dose combination ICS-formoterol as a controller for Step 1 in addition to the reliever[13].

We did not see a significant difference in asthma control when comparing patients in Step 3 with the Step 1 group. Steps 4 and 5 represent severe and difficult-to-treat asthma[13,14], which likely account for the significantly higher proportions of not well-controlled asthma in these steps compared with Step 1.

There are several strengths to our study that warrant mention. Our study was able to link systematically measured

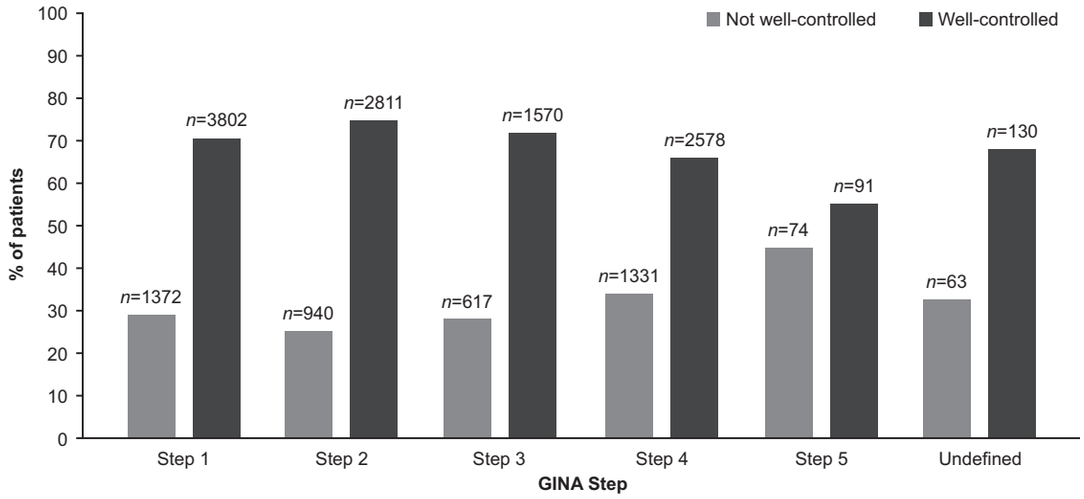

Fig. 3 Asthma control status of patients by GINA Step at index date. Percentage and number of individuals with 'Not well-controlled' and 'Well-controlled' asthma. GINA Global Initiative for Asthma.

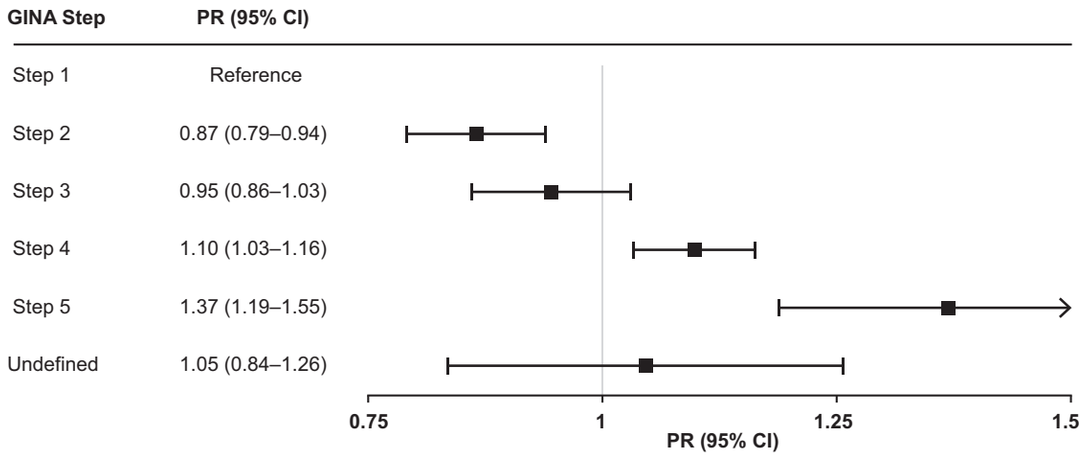

Fig. 4 Association between GINA Step and asthma control at index date. Adjusted prevalence ratio of 'Not well-controlled' asthma by GINA Step among the treated asthma population. CI confidence interval, GINA Global Initiative for asthma, PR prevalence ratio.

asthma symptom control via the ACT and prescription information in a real-world setting. We also had sufficient prescription information and history within Practice Fusion's EMR to calculate GINA Steps for our patient population, enabling us to describe burden of not well-controlled asthma among patients across all GINA Steps. Additionally, the use of this real-world data source allowed our study to identify a large number of patients with asthma, across the entire asthma continuum, with a mixture of asthma symptom control. Finally, we were able to demonstrate that the significant differences in asthma control at higher GINA Steps were maintained after adjusting for confounding.

Despite the variety and availability of asthma treatment, there are large numbers of patients with asthma that remain symptomatic across the treatment continuum in real-world primary care and specialist outpatient practices. Consequently, our study highlights the importance of assessing asthma symptom control at every opportunity; and evaluating treatment response, inhaler technique, adherence, and environmental exposures for patients with symptomatic asthma. There are several limitations to our study. The EHR data is intended for clinical decision making, not research. Thus, in using routinely collected healthcare data for research we must recognize the limitations in data quality. In addition, the Practice Fusion asthma patient population is an open cohort, in which patients may enter or leave care at any time. As such, while investigating changes in GINA Step over time may provide added insight into patients' asthma control status, the current study was limited by the data available in the Practice Fusion database.

Moreover, given that Practice Fusion is used primarily by smaller outpatient primary and specialist care offices in the US, it is likely that the asthma patient population in the Practice Fusion research database will be systematically different from the overall US asthma population which includes patients seen in large practices, inpatient facilities, or other healthcare settings. Indeed, patients in this study population were primarily of White or Unknown race, making it challenging to assess the impact of variables such as socioeconomic status and race/ethnicity on asthma control, which have previously been linked to asthma-related health outcomes[22–25]. Additionally, as the dataset does not include all levels of care (e.g., inpatient care) or data from large healthcare systems, the study population may represent patients with better control/less severe disease compared with a sample that included ACT measures from

across the healthcare continuum. Further, the ACT was administered by clinicians via a clinical decision support prompt in the EHR rather than self-administered by the patient. This process leads to the possibility of reporting bias as patient answers may reflect how they would like to be perceived by the clinician rather than their actual experience.

There are also limitations in using GINA Step categorization for research purposes. Prescriptions represent the intent of the prescriber not actual medication use or adherence. We assumed that patients took their prescription medications as prescribed. We were reliant on natural language processing of prescription signature information captured in the Practice Fusion database for the calculation of ICS daily dose; which may have incorrectly specified actual frequency and/or dosage. Due to the limitations with the prescription data in the Practice Fusion EHR, we cannot account for daily OCS that is typically used in calculating GINA Step 5. We had to assume that all OCS use was less than or equal to 28 days; and, consequently had no impact on GINA Step. Furthermore, it is worth noting that the current study did not differentiate between not well-controlled and poorly controlled asthma.

Lastly, our analysis did not assess the duration at which a patient was in a GINA Step. Given the nature of the EHR data, our patient population contained a mixture of patients that: (1) recently initiated asthma treatment (new users); (2) recently modified their previous asthma treatment; and 3() had used a specific asthma treatment for an extended period and were renewing the prescription that had been working for them (prevalent users). Our analysis was not able to distinguish between these three distinct groups of patients.

DATA AVAILABILITY

Anonymized individual participant data and study documents can be requested for further research from www.clinicalstudydatarequest.com.

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AUTHOR CONTRIBUTIONS

The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors, take responsibility for the integrity of the work as a whole, contributed to the writing and reviewing of the manuscript, and have given final approval for the version to be published. All authors take complete responsibility for the integrity of the data and accuracy of the data analysis. J.D., B.D., D.H., and L.S. were involved in the acquisition of data. J.D., B.D., S.Z., and L.S. were involved in the conception or design of the study and in data analysis or interpretation. J.C. was involved in data analysis or interpretation.

COMPETING INTERESTS

J.D., S.Z., J.C., D.H., L.S., B.D. declare no competing non-financial interests but the following competing financial interests: J.D., S.Z., and J.C. are employees of GSK and hold stocks/shares in GSK; D.H. and L.S. were employees of GSK and held stocks and shares at the time of the study; B.D. is a Ph.D candidate at UNC Chapel Hill and works as a research assistant at GSK.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41533-023-00338-7.

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REDUKSJON (RRR)
I RATEN AV MODERATE ELLER ALVORLIGE FORVERRINGER vs LAMA/LABA (formoterol/glykopyrrionium)[1]

(95% CI: 17, 31; p<0,0001).
Frekvens: 1,08 vs 1,42 hendelser/pasientår[1]
TRIXEO vs ICS/LABA (budesonid/formoterol) viste en reduksjon på 13%. RR: 0.87; (0.79–0.95), p=0,003[1]

20%
REDUKSJON (RRR)
AV ALVORLIGE FORVERRINGER (SOM RESULTERTE I SYKEHUSINNLEGGELSE ELLER DØD) VS ICS/LABA[1]

(95% CI: 3,34; p=0,002) sammenlignet med budesonid/formoterol MDI. Frekvens: 0,13 vs 0,16 hendelser pr. pasientår. Ingen reduksjon av sykehusinnleggelser eller død vs LAMA/LABA (formoterol/glykopyrrionium)[1]

NO-9654-10-2022-TRX

RRR: relative risikoreduksjon. ICS=inhalert kortikosteroid, LAMA=langtidsvirkende muskarinreseptorantagonist, LABA=langtidsvirkende beta2-agonist

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Modelling 30-day hospital readmission after discharge for COPD patients based on electronic health records

Meng Li[1,2,5], Kun Cheng[3,5], Keisun Ku[3], Junlei Li[1], Hao Hu[1,4]✉ and Carolina Oi Lam Ung[1,4]✉

Chronic Obstructive Pulmonary Disease (COPD) is the third most common chronic disease in China with frequent exacerbations, resulting in increased hospitalization and readmission rate. COPD readmission within 30 days after discharge is an important indicator of care transitions, patient's quality of life and disease management. Identifying risk factors and improving 30-day readmission prediction help inform appropriate interventions, reducing readmissions and financial burden. This study aimed to develop a 30-day readmission prediction model using decision tree by learning from the data extracted from the electronic health record of COPD patients in Macao. Health records data of COPD inpatients from Kiang Wu Hospital, Macao, from January 1, 2018, to December 31, 2019 were reviewed and analyzed. A total of 782 hospitalizations for AECOPD were enrolled, where the 30-day readmission rate was 26.5% (207). A balanced dataset was randomly generated, where male accounted for 69.1% and mean age was 80.73 years old. Age, length of stay, history of tobacco smoking, hemoglobin, systemic steroids use, antibiotics use and number of hospital admission due to COPD in last 12 months were found to be significant risk factors for 30-day readmission of CODP patients ($P < 0.01$). A data-driven decision tree-based modelling approach with Bayesian hyperparameter optimization was developed. The mean precision-recall and AUC value for the classifier were 73.85, 73.7 and 0.7506, showing a satisfying prediction performance. The number of hospital admission due to AECOPD in last 12 months, smoke status and patients' age were the top factors for 30-day readmission in Macao population.

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a major chronic disease characterized by slowly growing airflow obstruction[1], which was projected to be the third leading cause of death worldwide by 2030[2]. From 1990 to 2015, the global prevalence of COPD increased by 44.2%[3]. It is estimated that 328 million people have COPD worldwide[4]. In particular, there are approximately 99.9 million COPD patients in China, and more than 900,000 people die prematurely from COPD each year[5]. The incidence of COPD among the younger population (people aged 40 years old and over) estimated to be 13.7% is also increasing, posing substantial economic and social burden on both patients and healthcare systems[6]. COPD is often accompanied by exacerbations of respiratory symptoms requiring admission to the hospital, where the cost of hospitalizations accounts for 75% of the total direct healthcare cost for COPD[7]. Acute exacerbations of COPD (AECOPD) is defined as a sustained worsening of patient's symptoms from stable states, which is the most common cause of COPD-related hospitalizations[8].

As the condition of COPD deteriorates, many COPD patients experience loss of function and are subject to high risk of admitting to the hospital repeatedly[9]. Readmission is usually measured by a 30-day readmission (hospital revisits within 30 days after discharge), which has been continuously rising worldwide in the last decade. COPD is one of the diseases with the highest rate of readmission within 30 days, along with congestive heart failure and pneumonia[10]. One research in UK showed that nearly 1 in 5 patients with COPD exacerbations had readmission at least once within 30 days after discharge. Reducing readmission is one of the priorities for some health systems, as hospital will otherwise be imposed financial penalties. The U.S. Centers for Medicare and Medicaid Services included COPD into its Hospital Readmission Reduction Program in 2014, which applied additional fines to the hospital when the readmission rate of medical insurance patients is too high[11,12].

Considering the risk factors for COPD readmission remain largely unknown, more and more studies have predicted the risk of 30-day readmissions and developed predictive tools in recent years. Conventional methods based human experience may be paradigm to some extent[13]. However, these methods are also subject to a few limitations. For example, the experience may vary among physicians depending on different clinical backgrounds and experiences and may result in inconsistent decisions for the same case. The human experience is not easily transferable or adaptive when the characteristics of patients changes, which is particularly the case in qualitative experience[14]. Recently, the advantages of machine learning methods in predicting the prognosis of patients have received much attention, the key of which is to deal with a complex nonlinear relationship between predictor variables and outcome indicators to produce more reliable predictions[15–17]. The machine models are built in an automatic manner via labelled dataset and so are quantitative, transferable and adaptive. Despite these advantages, there are only a few studies on their ability to predict 30-days readmission after discharging due to COPD, especially in Asian countries and regions. In addition, different machine learning models have different levels of model interpretability, which is also of high interest in helping practitioners/clinicians understand how a specific decision is made in machine learning models. However, the studies focused on interpretable machine learning models

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(e.g., decision tree), which are closer to human decision-making processes is even rarer.

The aim of this study is to develop a predictive decision tree model based on the data from the electronic health record (EHR) system to define and predict the risk factors that affect the 30-day readmission of COPD patients in Macao. The findings would be beneficial to formulating specific suggestions that manage the controllable risk factors to prevent readmission, and therefore avoid the negative impact of patients' prognosis and reduce their medical costs and disease burden.

RESULTS

Descriptive statistics

A total of 782 hospitalizations for AECOPD were enrolled in this study. Among them, 207 (26.5%) were selected as derivation sample due to readmission after the discharge of 30 days. Then 207 records were randomly selected from the remaining data (73.5%) that were not re-admitted to the hospital. As a result, a balanced dataset including 207 records with readmission and 207 records without readmission was generated. Descriptive information for the balanced dataset was shown in Table 1. It followed from Table 2 (end of this document) that male accounted for 69.1%. The mean age is 80.73 years old, 14.25% and 49.28% of patients were current or previous smokers, only 11.59% of patients did not have any comorbidities, mean LOS in this study is 12.99 days. For the blood test results, 71.74% of patients were with blood eosinophils < 300 cells/μL. 34.06%, 56.28%, 8.70% of patients' Hemoglobin, WBC and Creatinine were within normal range. Regarding to clinical therapies, 47.58% and 76.57% used systemic steroids and antibiotics, respectively. 89.13% received oxygen therapy, and 85.99% did not receive NIV. Only 14.73% had pulmonary rehabilitation during hospitalization.

Feature selection

The quantitative results of KS test for continuous variable selection were also summarized in Table 3, where the third row "logical" indicates whether the null hypothesis was rejected by comparing the second-row "*p* value" against the significant level at $\alpha = 0.05$. It showed that both

Age and LOS were significant for readmission modelling.

The results of Chi-Square test for categorical variables were summarized in Table 4. It follows that the significant features (highlighted in bold) included Smoke, Hemoglobin, Steroid, Antibiotics and NoH-12. As a result, there are a total of 7 significant features being selected for the decision tree classifier construction, which include continuous variables (Age, LOS) and categorical variables (Smoke, Hemoglobin, Steroid, Antibiotics, NoH-12).

Preliminary classifier comparisons

The results of the preliminary classifier performance comparison were summarized in this part. In particular, there is a classifier App available in MATLAB, entitled "classificationLearner", where 22 typical classification models, including Decision trees, Logistic

Table 1. Inclusion variables included three categories in this study.

Patients' information	age, gender, history of tobacco smoking, number of comorbidities (NOC), length of stay (LOS), number of hospital admission due to COPD in last 12 months (NoH-12)
Blood tests	BEC, hemoglobin, WBC and creatinine
Clinical therapies	systemic steroids (prednisolone, dexamethasone, methylprednisolone) and antibiotics, oxygen therapy, NIV and PR and inhaled medications

Table 2. Demographic information.

Variables	*n* (%)	Variables	*n* (%)
Gender		**WBC (10^9/L)**	
Male	286 (69.0%)	Below normal range	6 (1.5%)
Female	128 (31.0%)	Normal range	233 (56.3%)
Age (years)		Above normal range	166 (40.1%)
Median (IQR)	82 (73-88)	Missing	9 (2.2%)
Mean (SD)	80.73 (10.1)	**Creatinine (μmol/L)**	
History of tobacco smoking		Below normal range	269 (65.0%)
No	148 (35.7%)	Normal range	36 (8.7%)
Yes	59 (14.3%)	Above normal range	82 (19.8%)
Quit	204 (49.3%)	Missing	27 (6.5%)
Missing	3 (0.7%)	**Systemic steroids**	
NoC		No	215 (51.9%)
0	48 (11.6%)	Yes	197 (47.6%)
1	102 (24.6%)	Missing	2 (0.5%)
2	117 (28.2%)	**Oxygen therapy**	
3	99 (23.9%)	No	42 (10.2%)
4 or more	48 (11.6%)	Yes	369 (89.1%)
LOS		Missing	3 (0.7%)
Median (IQR)	11.00 (6.0–17.0)	**Noninvasive ventilation**	
Mean (SD)	12.99 (8.6)	No	356 (86.0%)
NoH-12		Yes	56 (13.5%)
No	127 (30.6%)	Missing	2 (0.5%)
1–3 times	153 (37.0%)	**Pulmonary rehabilitation**	
More than 3 times	132 (31.9%)	No	351 (84.8%)
Missing	2 (0.5%)	Yes	61 (14.7%)
BEC (cells/uL)		Missing	2 (0.5%)
Below 300 cells/uL	297 (71.7%)	**30 days readmission**	
Above 300 cells/uL	108 (26.1%)	No	207 (50.0%)
Missing	9 (2.2%)	Yes	207 (50.0%)
Hemoglobin (g/L)		**Inhaled medications**	
Below normal range	254 (61.3%)	Group 1	74 (17.9%)
Normal range	141 (34.1%)	Group 2	79 (19.1%)
Above normal range	9 (2.2%)	Group 3	234 (56.5%)
Missing	10 (2.4%)	Group 4	27 (6.5%)
Antibiotics			
No	97 (23.4%)		
Yes	317 (76.6%)		

Note: BEC was put into "Below" and "Above" categories by using a threshold of 300 cells/μL; Hemoglobin, WBC was put into "Below", "Normal" and "Above" categories by using <4, 4–10 and >10, respectively. Creatinine was put into "Below", "Normal" and "Above" categories by considering gender difference (normal range for male: 53-106 μmol/L; normal range for female: 44–97 μmol/L). NoC was categorized into categorical variable [0,1,2,3,4+], where 4+ means there was 4 or 4+ comorbidities. While NoH-12 was transformed into three categories including [0, (1,2,3), (4,5,5+)].

Table 3. Result of KS test for continuous variable.

	Age	LOS
P-value	$3.52\ e^{-05}$	$4.82\ e^{-04}$
Logical	1	1

Table 4. Results of Chi-Square test for categorical variable.

	Gender	Smoke	NoC	BEC	Hemoglobin	WBC	Creatinine
P-value	0.20	**6.15e^{-06}**	0.15	0.93	**8.24e^{-04}**	0.68	0.30
	Steroid	**Antibiotics**	OT	NIV	PR	**NoH-12**	Inhaled Medications
P-value	**0.023**	**0.028**	0.19	0.77	0.21	**4.93e^{-16}**	0.470

Table 5. Comparation results of 22 classification models in term of accuracy via five-fold cross-validation in MATLAB "classificationLearner".

Decision trees			Logistic regression	Naïve Bayes		SVM	
Fine	Medium	Coarse	LR	Gaussian	Kernel	Linear	Quadratic
63.5%	69.1%	72.2%	66.7%	66.9%	68.1%	67.9%	63.8%
Support Vector Machines (SVM)				**Ensemble approaches**			
Cubic	Fine Gaussian	Medium Gaussian	Coarse Gaussian	Boosted	Bagged	RUS Boosted	
62.3%	63.3%	67.4%	65.7%	69.3%	65.0%	69.1%	
Neural Networks					**Kernel**		
Narrow	Medium	Wide	Bi-layered	Tri-layered	SVM	LR	
60.6%	58.5%	59.4%	60.9%	60.6%	56.0%	57.7%	

Regression (LR), Naïve Bayes, Support Vector Machines (SVM), Ensemble approaches, Neural Networks, and Kernel approaches can be quickly tested in term of accuracy. The comparative results in terms of accuracy via five-fold cross-validation were summarized in Table 5.

It followed from Table 5 that the decision tree model (unoptimized) possessed the best performance in term of accuracy and therefore was selected for further study in this work.

Decision tree classifier

Hyperparameter optimization. The results of decision tree modelling were then summarized. To automatically tune the hyperparameters of the decision tree model by Bayesian optimization, three key hyperparameters were considered, including MinLeafSize ([1, max(2, floor(NumObservations/2))]), MaxNumSplits ([1, max(2,NumObservations-1)]) and SplitCriterion (e.g. gdi, deviance). The maximum objective evaluations were chosen as 60. The objective functions against the function evaluations (i.e., iteration) were displayed in Fig. 1. By using the Bayesian hyperparameter optimization, the classification loss of decision tree was decreased from 29.2% to 26.1%.

Confusion matrix. The confusion matrix of the decision tree optimized by Bayesian approach was displayed in Fig. 2. The target and output class represent the ground truth class and the predicted class, respectively. The diagonal cells in green display the number/percentage of the correct classification, while the off-diagonal cells are where the misclassification happens. For No class (without readmission), 144 in green is TP and 46 in red is FP, 63 in red is FN and 161 in green is TN. So precision for No class is 144/ (144+ 46) = 75.8%, while recall for No class is 144/(144+63) = 69.6%. Similarly, precision and recall for Yes class are 71.9% and 77.8%. As a result, the mean precision and recall for the decision tree classifier are 73.9% and 73.7%. The cell at the bottom right displays the overall accuracy (73.7%). These metrics for the balanced training dataset implied an acceptable performance.

ROC and AUC. The ROC curve of the optimized decision tree was displayed in Fig. 3 with an AUC value of 0.7506, which showed the diagnostic ability of the binary classifier system as its discrimination threshold was varied. An AUC value of 0.7506 meant the developed model was considered to be acceptable.

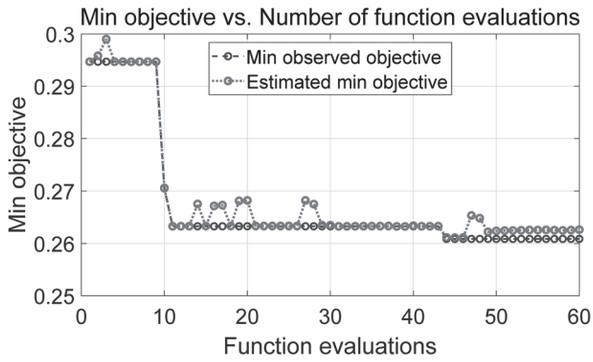

Fig. 1 Bayesian optimization loss of decision tree over function evaluations. Blue line represents the minimum observed objective and red line represents the estimated minimum objective.

Predictor importance. The predictor importance values returned by the optimized decision tree classifier could be obtained, where the most important variable in predicting readmission was the No of hospitalizations in the past 12 months, followed by smoking status and then age. While other variables, such as length of hospitalization stay, hemoglobin, steroid, antibiotics, although being selected in feature selection stage by using KS test (continuous variables) or Chi-Squared test (categorical variables), had very low importance estimates returned by the optimized decision tree.

Decision rules. The optimized decision tree was also displayed in Fig. 4 in a flowchart-like structure (a set of if-else conditions), where the paths from root to leaf represented the classification/prediction rules. In this figure, each node represented a test on a feature, each branch represented the outcome of the test, and each leaf (or terminal) node represented a class label. For example, the categorical variable NoH-12 was the root node, which was splitted into two branches. If its value fell into categorical 2 (more than 3 times), then the prediction was Yes, while if its value fell into categorical 0 and 1 (1–3 times), then the decision would go to smoke node for further test. It is believed that these if-else conditions in the decision tree model are easily understandable to human beings.

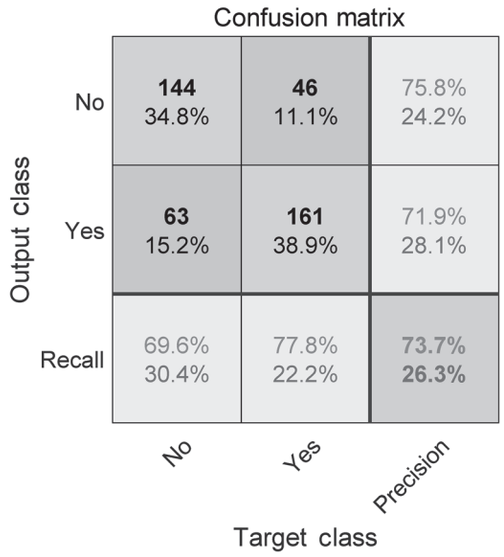

Fig. 2 Confusion matrix of the optimized decision tree model. Blue diagonal and red non-diagonal elements represent the correct and wrong prediction, respectively.

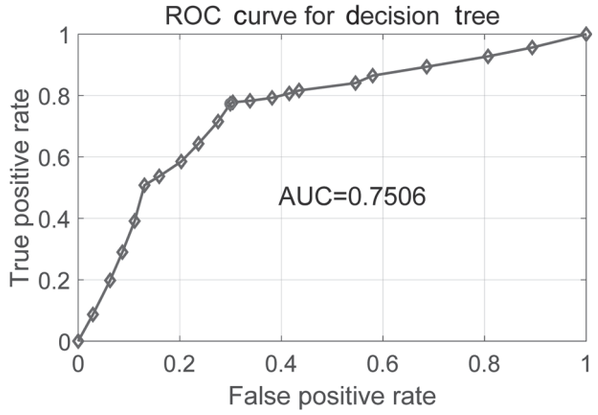

Fig. 3 ROC curve of the optimized decision tree. The blue line represents the pair of true positive rate against false positive rate and AUC value denotes the area under the ROC curve.

DISCUSSION

In this study, the readmission rate of COPD patients within 30 days of discharge was found to be 26.5%. A data-driven decision tree-based modelling approach with Bayesian hyperparameter optimization was developed. The key predictors of readmission included patients' comorbidities, the length of stay during previous admission, and the number of previous admissions. The mean precision-recall and AUC value for the decision tree classifier were 73.85%, 73.7% and 0.7506, showing a satisfying prediction performance. The similarities and differences of this study over the existing ones will be discussed in terms of readmission rate, contributing factors, and the model performance will be discussed further in the following.

The readmission rate of patients who readmitted to the hospital within 30 days of discharge from hospitalization due to COPD was 26.5%, which was slightly higher that the readmission rate found in another studies[17–21]. One study conducted in an Australian tertiary hospital found that the 30-days hospital readmission rate was 25%[19]. There are also serval studies focused on the 30-days readmission of COPD patients in the US. One research found that

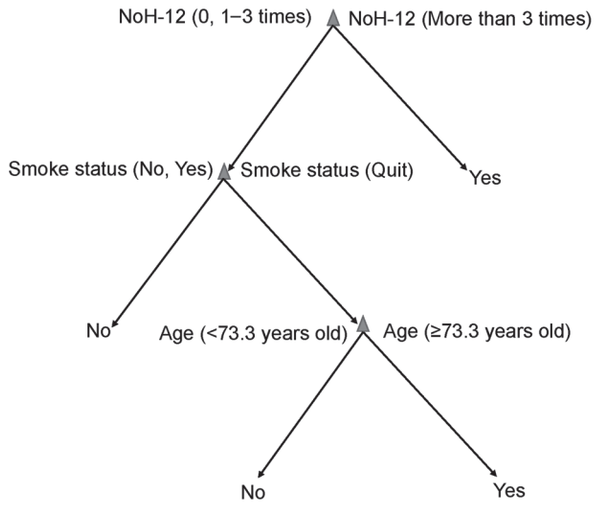

Fig. 4 Visualization of the decision tree in a flowchart-like structure. The decision rule has a hierarchical, tree structure consisting of a root node, branches, internal nodes and leaf nodes.

during 2003-2004, 22.6% of fee-for-service Medicare beneficiaries admitted to the hospital for COPD were readmitted within 30 days[20]. The readmission rates in similar studies in 2015 and 2019 were 20.2% and 21%, respectively[21]. In the United Kingdom, approximately a quarter (24%) of patients with COPD exacerbations were readmitted at least once within 30 days of discharge[22]. Researchers in London found that the 30-days readmission rate of AECOPD patients in London is between 14%-20%[23]. The higher readmission rate in this study may be partly explained by the age of the patients included in the studies. The patients in this study generally had a higher average age (80.73 years old) and most of them were combined with more than 1 type comorbidity (88.3%), indicating that the patients in this study might be subject to more serious health conditions contributing to a higher readmission rate.

Regarding the predictors of readmission after hospitalization, comorbidities, length of stay and previous admissions were frequently cited as predictors for readmission[24]. Regarding COPD-specific predictors analysis, Sharif et al found that history of heart failure, lung cancer, anxiety, depression, osteoporosis, and length of hospital stay were associated with higher likelihood of readmission within 30 days[25]. Poor lung functions like lower oxygen tension and dyspnea were identified as risk factors to COPD readmission[26]. COPD patients with acute hypercapnic respiratory failure, who had treatment with noninvasive ventilation have a higher risk of readmission and life-threatening events[27]. One study showed that weight loss during hospitalization and low body mass index were associated with unplanned readmission[28]. In addition to predictors related to high risk of readmission, a research in US found that any level of moderate or vigorous physical activity had a significantly lower risk of 30-day readmission compared with inactive patients by conducting multivariate adjusted analysis[29]. The use of nutritional supplementation for COPD inpatients was related to reduced 30 days readmission rate[30]. The risk factors affecting 30-day readmission of COPD patients in this study included NoH-12, smoking status, and patient's age, which were basically consistent with previous studies. Frequency of NoH-12 is closely linked to frequent COPD exacerbations, which requires hospital admission and is combined with a higher mortality[31]. The use of inhaled medications should be able to reduce exacerbations due to their benefits in reducing bronchospasm and inflammation, and relieving ongoing breathing problems[32,33]. On the other hand, it has also been shown that the use of inhaled medications were positively associated with a

longer length of stay during hospitalization[34], since the use of different inhaled medications was possibly associated with COPD severity as well. Nevertheless, the results in this study indicate that the use of different inhaled medications was not a significant factor for COPD readmission with 30 days after discharge. Further investigation is needed to explore the patients' compliance and the accuracy of the techniques when using the inhaled medications as the proper use of inhaled medications as prescribed have been shown to have an impact on both COPD exacerbations and COPD severity, which would in turn have effects on COPD readmission.

There was one significant inconsistency with other study findings in this study. Current smokers would not readmit to hospital within 30 days after discharge, which could be explained by the lower average age of current smoking group after in-depth investigation (current smoker: 74.83 years old, quitting smoking: 80.29 years old, non-smoker: 83.70 years old). This finding implied that the current smokers in our study might have a milder condition, because the number of comorbidities and risk of exacerbation increased with age[35]. Smoking had been proven to be the primary risk factor for COPD, causing irreversible damage to the lungs, so even patients who quit smoking still have a worse condition than patients who do not smoke[36]. Smoking cessation at an early stage of COPD should be taken as a priority when trying to improve COPD prognosis[37].

Based on previous studies, the LACE index is a common model used to assess the risk of a patient's 30-day readmission or death. The parameters include: Length of stay, acuity of admission, comorbidities, and emergency department visits within the last 6 months[19]. One research applied LACE index to COPD patients from 11 hospitals of Ontario during 2002-2004, where an AUC value of 0.684 was generated by the model[38]. Nevertheless, the results from another research in Australian shown that LACE index had moderate discriminative ability to predict 30-day readmission (AUC=0.63)[19]. Bashir et al found LACE index was not associated with readmission, and universal prediction model for readmission might not be achievable[39].

In this study, the overall accuracy is 73.7%, and AUC value of 0.7506. Although they are relatively high and acceptable, direct comparison of different predictive models is futile because the data-driven models will be changed according to data included, and the selection of parameters is also mutative. The advantages of this study can be summarized in the following aspects. Firstly, compared with traditional decision-making process conducted by physicians, machine learning methods are more consistent specific. Secondly, this research adopts a decision tree model with if-else conditions (or rules), which is easy to understand and interpret since it is like human decision-making process. Thirdly, the proposed framework integrating feature selection, decision tree classifier and Bayesian hyperparameter optimization is applicable to different classification problems in public health. This system could learn and self-improve and therefore more precise results will be recalculated when more new data is available. Finally, this is the first study on the readmission of COPD population in Macau with high-quality dataset, since the patient data is centralized, and rarely no patients were referred to another hospital for readmission.

Some limitations exist in this study mainly in terms of training data and modelling methods. In term of training data for model construction, most pulmonary function test data was either incomplete or unavailable in the EHR to allow categorization of the COPD patients according to the GOLD (Global Initiative for Chronic Obstructive Lung Disease) guideline. However, due to the included patients were all admitted for acute exacerbation of COPD, they were considered either Grade C or Grade D by the specialists; 2) we had a limited number of independent variables (features), and more clinical indicators including lung functions may provide a more accurate COPD readmission prediction; 3) at the same time, the sample size (e.g., number of observations) is relatively small, relevant studies will be carried out in the future to enlarge the training data for a more reliable prediction model; in addition, the prospective validation method, instead of the 5-fold cross-validation in the current study, can also be considered with the future advent of a relatively large labelled dataset. In term of modelling method in this study, 1) the current data-driven analysis and modelling approach could not present the causal relationship, which means the results may change by using various dataset (e.g., data with different characteristics); 2) although the decision tree model in this study is simple and relatively transparent, may not be able to be modelling very complex relationships between features and response variable. As a result, with the advent of a large amount of training dataset in the future, a more reliable (e.g., stable, accurate) modelling will be investigated by using more complex modelling methods (e.g., random forest).

Predictive models of readmission after discharge may serve as a tool that assists clinicians in developing treatment strategies specifically targeting those at a high risk of hospitalization and readmissions. A data-driven decision tree-based modelling approach with Bayesian hyperparameter optimization was developed for identifying discharged COPD patients with high risks of being readmitted within 30 days based on the health records of COPD inpatients from the EHR system of Kiang Wu Hospital, Macao. More clinical and lung conditions data are needed to expand the implications of this research. A set of if-else conditions were generated by the decision tree model with an overall accuracy of 73.7%, and an AUC of 0.7506. Moreover, the predictor importance values returned by the optimized decision tree classifier showed that the top factor for the readmission was the number of hospital admission due to AECOPD in last 12 months, followed by smoke status and patients' age. Reducing readmission rate could lead to less administrative burden and benefit to reduce patients' economic burden and quality of life. It is necessary for COPD patients to start smoking cessation in an early stage to reduce potential risks of readmission and related disease burden.

METHODS

Data collection

Obstructive airway disease is one of the ten leading causes of death in Macao. Studies have shown that second-hand smoke affects 14% of the local labor force, increasing the incidence and mortality of COPD in Macao. Kiang Wu is one of the three major hospitals in Macao, which accounts for 47% of total resources. In this study, we reviewed the health records of COPD inpatients from the EHR system of Kiang Wu Hospital from January 1, 2018, to December 31, 2019. The criteria of inclusion were: (1) patients admitted with a main diagnosis of COPD (International Classification of Diseases-10 codes (ICD-10): J44); and (2) admission due to acute exacerbation as confirmed by the specialists. It is noted that the labeled data and also the trained prediction model in the study is site-specific for regions with similar patient characteristics, although the overall methodology is transferable to other regions or studies.

Variables and measurements

There were 3 categories of data in this study including demographic data, blood test results and clinical therapies (See Table 1). Patients' demographic data included age, gender, history of tobacco smoking, number of comorbidities (NoC) and number of hospitalizations in the past 12 months (NoH-12). Blood test results included blood eosinophil count (BEC), hemoglobin, white blood cells (WBC) and creatinine. Clinical therapies for COPD in Macao included data about the usage of systemic steroids (prednisolone, dexamethasone, methylprednisolone) and antibiotics, oxygen therapy, noninvasive

ventilation (NIV) and pulmonary rehabilitation (PR). It is noted that there are too many combinations of inhaled medications and so it would be inappropriate to directly treat it as a categorical variable considering the limited number of samples in this study. Therefore, we divide the inhaled medications into a few categories. Following the work[34], according to the use of inhaled medications of the COPD, the hospitalization records were assigned to 1 of the 4 groups. Group 1 included the records who used only one type of inhaled medication (e.g., "LABA, LAMA or both", "SABA, SAMA or both" or ICS only.). Group 2 included the records who received two types of inhaled medications (e.g., "(LABA, LAMA or both) and (SABA, SAMA or both)", "(LABA, LAMA or both) and ICS" or "(SABA, SAMA or both) and ICS".). Group 3 included the records who used the combination of all 3 types of inhaled medications (e.g., "(LABA, LAMA or both) and (SABA, SAMA or both) and ICS"). Group 4 referred to the records in which the patients did not use any inhaled medications. It is noted that some variables such as BEC, hemoglobin, WBC, creatinine are indeed varied at every admission for an individual patient due to illness or drug effects, and therefore, this study used data on hospitalization information per patient admission to reflect the dynamic readmission risk.

Data discretization and balancing

Some continuous variables (e.g., BEC, hemoglobin, WBC, creatinine, NoC, NoH-12) were first transformed into categorical variables based on their proper reference ranges. Data imbalance problem, the distribution of examples across different classes is biased or skewed, generally poses a challenge for predictive modelling that the predictive performance is usually poor, specifically for the minority classes (the ones with fewer samples). Considering that in this study the numbers of records with readmission (Yes class) and without readmission (No class) were significantly different, data balancing technique was conducted to generate a balanced dataset for data-driven classification model construction. In particular, down-sampling approach was adopted in this study. In this approach, all records of Yes class (the one with fewer samples) were first preserved, then random sampling was performed by using "randperm" function (i.e., random permutation of integers) in MATLAB R2020b for the records of No class so that the number of randomly sampled records of No class had the same size as the Yes class. Therefore, a balanced dataset consisting of the same number of records for Yes and No classes was generated for the following data analysis and classification model construction.

Data analysis and feature selection

Descriptive analysis. Descriptive analysis was first performed for the continuous variables and categorical variables in the balanced dataset. In particular, for continuous variables, mean and median were adopted, while for categorical variables the number and proportion for different classes were summarized.

Feature selection. Considering that there was 15+ features (i.e., candidate independent variables) and a limited number of available samples (i.e., No. of records) for model construction, feature selection was performed to remove the irrelevant and redundant features so that a simpler and more reliable model can be derived for prediction. The feature selection methods for continuous and categorical variables were introduced below.

For continuous variables, in order to assess their distribution differences under Yes and No classes, the two-sample Kolmogorov-Smirnov test (KS test) was adopted. KS test is a general nonparametric statistical approach to quantify whether two samples come from the same distribution or not. Suppose two samples of size m and n with the observed/empirical cumulative distribution functions F(x) and G(x), the KS statistic is defined by

$$D_{m,n} = \sup_x |F_m(x) - G_n(x)| \quad (1)$$

where sup is the supremum function. The null hypothesis is that the samples are drawn from the same distribution, and one rejects the null hypothesis (at a significant level α) if $D_{m,n} > D_{m,n,\alpha}$ where $D_{m,n,\alpha}$ is the so-called critical value. For sufficient large m and n,

$$D_{m,n,\alpha} = c(\alpha)\sqrt{\frac{m+n}{mn}} \quad (2)$$

where c(α) is the inverse of the Kolmogorov distribution at α, given by $c(\alpha) = \sqrt{-0.5 * \ln(\alpha/2)}$. In this study, the "kstest2" function in MATLAB R2020b was adopted with $\alpha = 0.05$.

For categorical variables, Chi-Square test of independence was adopted. Chi-Square test is a statistical hypothesis test that assumes (the null hypothesis) the observed frequencies for a categorical variable match the expected frequencies for the categorical variable, i.e., H_0: "variable 1 is independent of variable 2". Therefore, it is usually used to determine whether there is an association between two categorical variables or not. In this study, Chi-Square statistics (along with its p-value) between the candidate categorical variables and the dependent variable (readmission or not) were returned by using the "crosstab" function (e.g., cross-tabulation) in MATLAB R2020b.

Classification model

Decision tree model. Upon choosing the features, the next step is to build a classification model by using machine learning approaches. Different machine learning-based classification models are available in literature such as classification tree, logistic regression, Naïve Bayes, Support Vector Machines (SVM), Ensemble approaches, Neural Network among others. Different models have their own pros and cons in terms of accuracy, computation load, transparency, interpretability and reliance on a large labelled dataset. In this study, upon a preliminary performance comparison in term of accuracy via five-fold cross-validation in MATLAB App "classificationLearner", decision tree model, a so-called white box model (against black-box or grey box models), is adopted. In particular, the main rationale for choosing the decision tree model are also summarized as below. First, in the preliminary performance comparison, decision tree-based approach possesses the best performance in term of accuracy. Second, decision tree is simple to understand and interpret since its inherent transparency and interpretability can help users follow the path of the tree and therefore understand the decision rules (i.e., if-else rules). Third, the simplicity of the model also makes it have a less reliance on a large training dataset compared against complex models such as neural network models. Fourth, predictor importance values can also be estimated in the decision tree, which can be used to assess the importance of different variables in making the decision. It is also noted that the missing data problem in the training dataset can be automatically handled by the decision tree model (e.g., "fitctree" in MATLAB environment).

Like many other machine learning models, there are hyperparameters in decision tree algorithm which have effects on its performance and should be properly tuned. The hyperparameters include the ones controlling the tree depth (e.g., MaxNumSplits, MinLeafSize or MinParentSize) and Split Criterion (e.g., gdi, deviance). Different approaches (e.g., grid search, random search, Bayesian optimization) are available to systematically tune these hyperparameters in order to get satisfying performance; in this study Bayesian parameter optimization (a sequential model-based optimization) was adopted due to its promising performance (efficiency) in deriving a good solution in a limited amount of steps/time. In addition, 5-fold cross-validation (against hold-out validation) was adopted to maximally use the limited amount of

dataset, gain stable predictions and also avoid the problem of overfitting (i.e., gaining good performance on the training dataset but poor performance on testing dataset). The decision tree algorithm with Bayesian hyperparameter optimization is summarized in supplementary martials.

Performance evaluation. Metrics to evaluate the performance of machine learning classification models are also introduced in this part. True Positive (TP) denotes the correctly predicted positive values; False Positive (FP) is the scenario where the actual class is negative, but the predicted class is positive; and False Negative (FN) represents the scenario that the actual class is positive, but the predicted class is negative. From these definitions, different metrics can then be defined for performance evaluation. For instance, Accuracy is a good measure for symmetric datasets (i.e., the number of each class has the same order of magnitude). Precision and Recall are also commonly used for performance evaluation, particularly for data with uneven class distribution. These values are usually first calculated for each class, and their mean values for different classes are then chosen. Accuracy, Precision and Recall for a specific class are defined by formula below (3), which can be calculated by using confusion matrix.

$$Accuracy = \frac{\sum TP}{ALL},\ Precision = \frac{TP}{TP + FP},\ Recall = \frac{TP}{TP + FN} \quad (3)$$

A receiver operating characteristic curve (also termed ROC curve) is a graphical plot illustrating the classification ability of a binary classifier, where the true positive rate against the false negative rate is plotted at various thresholds (for classification). Upon plotting ROC, area under the ROC curve (AUC) is an effective manner to summarize the overall accuracy, which takes value from 0 to 1. In general, an AUC of 0.5 suggests no discrimination, and 0.7 to 0.8 is considered acceptable, 0.8 to 0.9 is considered excellent, and more than 0.9 is considered outstanding[18].

Reporting summary

Further information on research design is available in the Nature Research Reporting Summary linked to this article.

DATA AVAILABILITY

The data that support the findings of this study are available on request from the corresponding author [COLU].

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AUTHOR CONTRIBUTIONS

M.L., K.C., C.O.L.U., and H.H. conceived and designed this study. K.K. and J.L. acquired and collected the data. M.L. performed data analysis, ML, KC and JL drafted the first version of the manuscript. All authors revised the manuscript and approved the final version submitted. All authors had full access to all the data in this study and accept responsibility to submit for publication. M.L. and K.C. are co-first author, contributing equally to this work.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical approval for this study was obtained from the ethical review committee at the Kiang Wu Hospital, Macao [Ref. No. 2019-015] with a waiver regarding informed consent, because all data were retrospectively collected and anonymized in the standardized case report form of the hospital. It was also confirmed that all data collection was performed in accordance with relevant guidelines and regulations.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41533-023-00339-6.

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ORION PHARMA

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INHALASJONSPULVER 80 mikrogram/4,5 mikrogram, 160 mikrogram/4,5 mikrogram og 320 mikrogram/9 mikrogram: Hver avgitte dose inneh.: Budesonid 80 mikrogram, resp. 160 mikrogram og 320 mikrogram, formoterolfumaratdihydrat 4,5 mikrogram, resp. 4,5 mikrogram og 9 mikrogram, laktose. **Indikasjoner: 80 mikrogram/4,5 mikrogram:** Astma: Voksne, ungdom og barn ≥6 år: Regelmessig behandling ved behov for kombinasjon av langtidsvirkende β_2-reseptoragonist og inhalasjonskortikosteroid: For pasienter hvor inhalasjonskortikosteroid og korttidsvirkende β_2-reseptoragonister ved behov ikke gir tilstrekkelig kontroll av sykdommen, samt pasienter hvor inhalasjonskortikosteroid kombinert med langtidsvirkende β_2-reseptoragonister allerede gir tilstrekkelig kontroll av sykdommen. Ikke egnet til bruk ved alvorlig astma. **160 mikrogram/4,5 mikrogram og 320 mikrogram/9 mikrogram:** Astma: Voksne og ungdom ≥12 år: Regelmessig behandling ved behov for kombinasjon av langtidsvirkende β_2-reseptoragonist og inhalasjonskortikosteroid: For pasienter hvor inhalasjonskortikosteroid og korttidsvirkende β_2-reseptoragonister ved behov ikke gir tilstrekkelig kontroll av sykdommen, samt pasienter hvor inhalasjonskortikosteroid kombinert med langtidsvirkende β_2-reseptoragonister allerede gir tilstrekkelig kontroll av sykdommen. Kronisk obstruktiv lungesykdom (kols): Voksne ≥18 år: Symptomatisk behandling av kols-pasienter med FEV_1 (forsert ekspiratorisk volum i 1 sekund) <70% av forventet normalverdi (postbronkodilatator) og en eksaserbasjonshistorikk på tross av regelmessig bronkodilaterende behandling. **Dosering:** Astma: Ikke beregnet for initialbehandling ved astma. Behandlingen individualiseres og tilpasses sykdommens alvorlighetsgrad, både ved behandlingsstart og når vedlikeholdsdosen justeres. Ved behov for behandling i tillegg til kombinasjonsinhalatoren, bør passende dose av β_2-reseptoragonist og/eller kortikosteroid forskrives i separat inhalator. Dosen bør titreres til laveste dose som gir symptomkontroll. Pasienten bør følges jevnlig opp av lege/helsepersonell slik at dosen forblir optimal. Når langtids symptomkontroll er oppnådd med laveste anbefalte dose, kan inhalasjonskortikosteroid forsøksvis gis alene. **Vedlikeholdsbehandling:** Brukes regelmessig, med en separat, hurtigvirkende bronkodilatator som akuttmedisin. Pasienten bør rådes til å ha separat hurtigvirkende bronkodilatator tilgjengelig for akuttbruk til enhver tid. Vanligvis oppnås symptomkontroll med dosering 2 ganger daglig. Ved titrering til laveste effektive dose, er det mulig å forsøke dosering 1 gang daglig, når legen vurderer at en langtidsvirkende bronkodilatator i kombinasjon med et inhalasjonskortikosteroid er nødvendig for å opprettholde kontroll. Økt bruk av separat hurtigvirkende bronkodilatator tyder på forverring av underliggende sykdom og krever ny vurdering av behandlingen. **80 mikrogram/4,5 mikrogram:** Voksne ≥18 år: 1-2 inhalasjoner 2 ganger daglig. Enkelte kan ha behov for opptil maks. 4 inhalasjoner 2 ganger daglig. Ungdom 12-17 år: 1-2 inhalasjoner 2 ganger daglig. Barn ≥6 år: 2 inhalasjoner 2 ganger daglig. Barn <6 år: Anbefales ikke. **160 mikrogram/4,5 mikrogram:** Voksne ≥18 år: 1-2 inhalasjoner 2 ganger daglig. Enkelte kan ha behov for opptil maks. 4 inhalasjoner 2 ganger daglig. Ungdom 12-17 år: 1-2 inhalasjoner 2 ganger daglig. Barn ≥6 år: Se 80 mikrogram/4,5 mikrogram. Barn <6 år: Anbefales ikke. **320 mikrogram/9 mikrogram:** Skal kun brukes til vedlikeholdsbehandling. Voksne ≥18 år: 1 inhalasjon 2 ganger daglig. Enkelte kan ha behov for opptil maks. 2 inhalasjoner 2 ganger daglig. Ungdom 12-17 år: 1 inhalasjon 2 ganger daglig. Barn ≥6 år: Se 80 mikrogram/4,5 mikrogram. Barn <6 år: Anbefales ikke. **Vedlikeholds- og anfallskuperende behandling:** Daglig vedlikeholdsdose og i tillegg ved behov. Preparatet bør være tilgjengelig for akuttbruk. For pasienter som tar Bufomix Easyhaler som symptombehandling skal lege og pasient diskutere forebyggende behandling med Bufomix Easyhaler mot allergen- eller anstrengelsesutløst bronkokonstriksjon. Anbefalt bruk skal ta hensyn til hyppigheten av behovet. Ved hyppig behov for bronkodilatasjon uten korresponderende behov for en økt dose av inhalerte kortikosteroider bør annen symptombehandling brukes. Vedlikeholds- og anfallskuperende behandling bør vurderes spesielt ved utilfredsstillende astmakontroll og hyppig behov for anfallskuperende behandling, og når tidligere astmaeksaserbasjoner har krevd medisinsk behandling. Tett oppfølging av doserelaterte bivirkninger er nødvendig hos pasienter som tar et høyt antall inhalasjoner ved behov. **80 mikrogram/4,5 mikrogram:** Voksne og ungdom ≥12 år: Anbefalt vedlikeholdsdose er 2 inhalasjoner daglig, enten 1 morgen og 1 kveld eller 2 inhalasjoner enten morgen eller kveld. Ved symptomer kan 1 tilleggsinhalasjon tas ved behov. Dersom symptomene vedvarer etter noen minutter, bør det tas 1 tilleggsinhalasjon. Det bør ikke tas >6 inhalasjoner ved ett enkelt doseringstilfelle. Det er vanligvis ikke nødvendig med >8 inhalasjoner daglig. Det kan likevel brukes inntil 12 inhalasjoner daglig i en begrenset periode. Ved bruk av >8 inhalasjoner daglig bør lege kontaktes. Pasienten bør undersøkes og vedlikeholdsdosen revurderes. Barn <12 år: Anbefales ikke. **160 mikrogram/4,5 mikrogram:** Voksne og ungdom ≥12 år: Anbefalt vedlikeholdsdose er 2 inhalasjoner daglig, enten 1 morgen og 1 kveld eller 2 inhalasjoner enten morgen eller kveld. For noen kan en vedlikeholdsdose på 2 inhalasjoner 2 ganger daglig være nødvendig. Ved symptomer kan 1 tilleggsinhalasjon tas ved behov. Dersom symptomene vedvarer etter noen minutter, bør det tas 1 tilleggsinhalasjon. Det bør ikke tas >6 inhalasjoner ved ett enkelt doseringstilfelle. Det er vanligvis ikke nødvendig med >8 inhalasjoner daglig. Det kan likevel brukes inntil 12 inhalasjoner daglig i en begrenset periode. Ved bruk av >8 inhalasjoner daglig bør lege kontaktes. Pasienten bør undersøkes og vedlikeholdsdosen revurderes. Barn <12 år: Anbefales ikke. **Kols: 160 mikrogram/4,5 mikrogram:** Voksne: 2 inhalasjoner 2 ganger daglig. **320 mikrogram/9 mikrogram:** Voksne: 1 inhalasjon 2 ganger daglig. **Spesielle pasientgrupper:** Nedsatt lever-/nyrefunksjon: Data mangler. Økt eksponering av budesonid og formoterol kan forventes ved alvorlig levercirrhose. Barn <6 år: Anbefales ikke. Eldre: Dosejustering ikke nødvendig. **Administrering:** Til inhalasjon. For bruksanvisning, se SPC og pakningsvedlegg. For å minske risiko for soppinfeksjon i munn/svelg bør munnen skylles med vann etter hver vedlikeholdsdosering. Ved soppinfeksjon i munn/svelg, bør munnen skylles med vann også etter anfallskuperende behandling. Pasienten skal inhalere hurtig og kraftig, og ikke puste ut i apparatet. **Kontraindikasjoner:** Overfølsomhet for innholdsstoffene. **Forsiktighetsregler:** Dosen bør trappes gradvis ned ved seponering, og behandling bør ikke avsluttes brått. Fullstendig seponering av inhalerte kortikosteroider bør unngås, med mindre det er midlertidig behov for å bekrefte diagnosen astma. Dersom pasienten mener behandlingen ikke er effektiv eller bruker flere doser enn høyeste anbefalte dose, skal lege oppsøkes. Plutselig og tydelig forverring av astma eller kols er potensielt livstruende, og pasienten trenger umiddelbar medisinsk utredning. Det skal vurderes om det er behov for å øke behandling med kortikosteroider, f.eks. orale kortikosteroider, eller antibiotikabehandling ved infeksjon. Pasienten bør minnes på å ta vedlikeholdsdosen som forskrevet, også ved symptomfrihet. Når astmasymptomene er under kontroll bør det vurderes en gradvis nedtrapping av dosen. Det er viktig med regelmessig vurdering ved nedtrapping. Alvorlige astmarelaterte bivirkninger og eksaserbasjoner kan oppstå. Behandling skal ikke initieres under en eksaserbasjon, eller ved signifikant eller akutt forverring av astma. Pasienten skal rådes til å fortsette behandlingen, men kontakte lege ved ukontrollerte eller forverrede astmasymptomer. Studiedata mangler for kols-pasienter med FEV_1 >50% av forventet normalverdi pre-bronkodilatator og med FEV_1 <70% av forventet normalverdi post-bronkodilatator. Paradoksal bronkospasme: Kan oppstå og gi umiddelbar økning i pipende/hvesende pust og andpustenhet. Preparatet skal da seponeres umiddelbart, pasienten vurderes, og alternativ behandling startes om nødvendig. Paradoksal bronkospasme responderer på hurtigvirkende inhalert bronkodilatator og bør behandles umiddelbart. Systemiske effekter: Systemiske effekter av inhalasjonskortikosteroider kan forekomme, spesielt ved høye doser over lengre tid. Effektene er trolig avhengige av dose, eksponeringstid, samtidig og tidligere steroideksponering og individuell følsomhet. Synsforstyrrelser er sett ved bruk av systemiske og topikale kortikosteroider. Ved synsforstyrrelser, inkl. tåkesyn, skal pasienten vurderes for henvisning til øyelege for vurdering av årsaker, inkl. grå/grønn stær eller sentral serøs chorioretinopati (CSCR), som er rapportert ved bruk. Potensielle effekter på bentetthet bør vurderes, spesielt hos pasienter med samtidige risikofaktorer for osteoporose, og som bruker høye doser over lengre perioder. Langtidsbruk av inhalert budesonid med gjennomsnittlige daglige doser på 400 mikrogram til barn og 800 mikrogram til voksne, har ikke vist signifikant effekt på benmineraltettheten. Ved mistanke om nedsatt binyrebarkfunksjon pga. tidligere systemisk steroidbehandling, bør forsiktighet utvises ved behandlingsstart. Inhalert budesonid vil normalt minimere behovet for orale steroider, men ved overføring fra orale steroider er det risiko for vedvarende redusert binyrerespons. Etter avsluttet behandling med orale steroider, kan pasienter med oral steroidavhengighet som overføres til inhalert budesonid, ha risiko for nedsatt binyrebarkfunksjon i lengre tid. I slike tilfeller bør HPA-aksens funksjon overvåkes jevnlig. Langvarig behandling med høye doser inhalasjonskortikosteroider, spesielt doser høyere enn anbefalt, kan også gi klinisk signifikant binyrebarkssuppresjon. Ytterligere systemisk kortikosteroiddekning bør derfor vurderes i perioder med stress, som ved alvorlige infeksjoner eller elektiv kirurgi. Rask reduksjon av steroiddosen kan indusere akutt adrenerg krise. Behandling med supplerende systemiske steroider eller inhalert budesonid bør ikke avbrytes brått. Overgang fra oral behandling vil gi en generelt lavere systemisk steroidvirkning, noe som kan gi allergiske eller artrittiske symptomer som rhinitt, eksem og muskel-/leddsmerter. Spesifikk behandling bør innledes ved disse lidelsene. En generell utilstrekkelig glukokortikoideffekt bør mistenkes ved symptomer som tretthet, hodepine, kvalme og brekninger. Det kan da være nødvendig med midlertidig økning av den orale glukokortikoiddosen. Pneumoni ved kols: Økt forekomst av pneumoni, inkl. pneumoni som krever sykehusinnleggelse, er sett hos kols-pasienter som bruker inhalasjonskortikosteroider. Vær oppmerksom på mulig utvikling av pneumoni hos kols-pasienter, da kliniske tegn kan ligne symptomer på kols-eksaserbasjoner. Risikofaktorer inkluderer røyking, høy alder, lav BMI og alvorlig kols. Annet: Forsiktighet bør utvises ved tyreotoksikose, feokromocytom, diabetes mellitus, ubehandlet hypokalemi, hypertrofisk obstruktiv kardiomyopati, idiopatisk subvalvulær aortastenose, alvorlig hypertensjon, aneurisme eller andre alvorlige hjerte-karlidelser som iskemisk hjertesykdom, takyarytmier eller alvorlig hjertesvikt. Formoterol kan indusere forlenget QT_C-intervall. Forsiktighet bør utvises ved forlenget QT_C-intervall. Behov for inhalasjonskortikosteroid, samt dose, bør revurderes hos pasienter med aktiv eller sovende lungetuberkulose, sopp- og virusinfeksjon i luftveiene. Potensielt alvorlig hypokalemi kan oppstå ved høye doser β_2-reseptoragonister. Samtidig behandling med legemidler som kan indusere hypokalemi eller potensere hypokalemisk effekt kan forsterke den mulige hypokalemiske effekten. Spesiell forsiktighet bør utvises ved ustabil astma ved varierende bruk av bronkodilatator som akuttmedisin, ved akutt alvorlig astma da tilhørende risiko kan forsterkes pga. hypoksi, og ved andre tilstander der sannsynlighet for hypokalemi er økt. I slike tilfeller bør serumkaliumnivået følges. Ekstra blodsukkermåling bør vurderes hos diabetikere. Candidainfeksjon i orofarynks skyldes legemiddeldeponering. Orofaryngeal candidainfeksjon responderer ofte på lokal antifungal behandling uten at det er nødvendig å seponere inhalasjonskortikosteroidet. Inneholder små mengder melkeprotein som kan forårsake allergiske reaksjoner. Barn og ungdom: Ved langstidsbehandling med inhalasjonskortikosteroider til barn anbefales det at høyden måles regelmessig. Ved langsom vekst bør behandlingen gjennomgås mtp. dosereduksjon til laveste, effektive dose. Fordel av kortikosteroidbehandling skal vurderes nøye opp mot risiko for veksthemming. Henvisning til pediatrisk lungespesialist bør også vurderes. Langtidsdata tyder på at de fleste barn og unge som behandles med budesonid til inhalasjon til slutt når sin normalhøyde som voksne. Det er sett en liten, men forbigående, reduksjon i vekst (ca. 1 cm). Dette oppstår vanligvis i løpet av første behandlingsår. **Interaksjoner:** For utfyllende informasjon om relevante interaksjoner, bruk interaksjonsanalyse. Potente CYP3A-hemmere vil trolig gi en betydelig økning i plasmanivå av budesonid, og samtidig bruk bør unngås. Dersom dette ikke er mulig, bør tidsintervallet mellom administrering av hemmer og budesonid være lengst mulig. Vedlikeholdsbehandling og anfallskuperende behandling anbefales ikke ved bruk av CYP3A-hemmere. Samtidig behandling med CYP3A-hemmere forventes å øke risiko for systemiske bivirkninger. Kombinasjon bør unngås med mindre fordel oppveier økt risiko for systemiske bivirkninger av kortikosteroider. I slike tilfeller skal pasienten overvåkes for systemiske kortikosteroideffekter. Betablokkere (inkl. øyedråper) kan svekke eller hemme effekten av formoterol, og bør derfor ikke gis samtidig dersom det ikke er helt nødvendig. Samtidig behandling med kinidin, disopyramid, prokainamid, fentiaziner, antihistaminer (terfenadin) og TCA kan forlenge QT_C-intervallet og øke risiko for ventrikulære arytmier. Levodopa, levotyroksin, oksytocin og alkohol kan nedsette kardial toleranse for β_2-reseptoragonister. Samtidig behandling med MAO-hemmere, inkl. legemidler med tilsvarende egenskaper, kan utløse hypertensive reaksjoner. Forhøyet risiko for arytmier ved samtidig anestesibehandling med halogenerte hydrokarboner. Samtidig bruk av andre betaadrenerge eller antikolinerge legemidler kan ha mulig additiv bronkodilaterende effekt. Behandling med β_2-reseptoragonist kan gi hypokalemi, som kan forsterkes av samtidig behandling med xantin-derivater, kortikosteroider og diuretika. Hypokalemi kan øke risikoen for arytmier ved samtidig bruk av digitalisglykosider. **Graviditet, amming og fertilitet:** Graviditet: Bør kun brukes under graviditet når nytte oppveier potensiell risiko. Lavest effektive budesonoddose bør brukes. Dyrestudier viser at prenatal påvirkning av glukokortikoider øker risiko for intrauterin veksthemming, kardiovaskulær sykdom hos voksne og permanent endring i tetthet av glukokortikoide reseptorer, nevrotransmitteromsetning og atferd, ved eksponering under det teratogene doseringsintervallet. Amming: Det bør vurderes om fordelen for moren er større enn mulig risiko for barnet. Budesonid: Utskilles i morsmelk. Det forventes ingen effekter av budesonid hos diende barn der mor behandles med terapeutiske doser. Formoterol: Overgang i morsmelk er ukjent. Fertilitet: Formoterol kan gi noe redusert fertilitet hos hannrotte ved høy systemisk eksponering. **Bivirkninger:** Vanlige (≥1/100 til <1/10): Hjerte/kar: Palpitasjoner. Infeksiøse: Candidainfeksjoner i orofarynks, pneumoni (kols-pasienter). Luftveier: Mild irritasjon i halsen, hoste, heshet. Nevrologiske: Hodepine, tremor. Mindre vanlige (≥1/1000 til <1/100): Gastrointestinale: Kvalme. Hjerte/kar: Takykardi. Hud: Blåmerker. Muskel-skjelettsystemet: Muskelkramper. Nevrologiske: Svimmelhet. Psykiske: Aggresjon, psykomotorisk hyperaktivitet, angst, søvnforstyrrelser. Øye: Tåkesyn. Sjeldne (≥1/10 000 til <1/1000): Hjerte/kar: Hjertearytmier, f.eks. atrieflimmer, supraventrikulær takykardi, ekstrasystoler. Immunsystemet: Umiddelbare og forsinkede overfølsomhetsreaksjoner, f.eks. eksantem, urticaria, pruritus, dermatitt, angioødem og anafylaktisk reaksjon. Luftveier: Bronkospasme. Stoffskifte/ernæring: Hypokalemi. Svært sjeldne (<1/10 000): Endokrine: Cushings syndrom, binyresuppresjon, veksthemming, nedsatt benmineraltetthet. Hjerte/kar: Angina pectoris, forlenget QT_C-intervall, blodtrykksvariasjoner. Nevrologiske: Smaksforstyrrelser. Psykiske: Depresjon, atferdsrelaterte endringer (primært hos barn). Stoffskifte/ernæring: Hyperglykemi. Øye: Katarakt, glaukom. Ukjent frekvens: Behandling med β_2-reseptoragonister kan gi økt nivå av insulin, frie fettsyrer, glyserol og ketonlegemer i blodet. Økt mottakelighet for infeksjoner og nedsatt evne til å tilpasse seg stress kan også forekomme. **Overdosering/Forgiftning:** Symptomer: Formoterol: Tremor, hodepine, palpitasjoner. Det er sett isolerte tilfeller av takykardi, hyperglykemi, hypokalemi, forlenget QT_C-intervall, arytmier, kvalme og oppkast. Budesonid: Ved kronisk bruk i høye doser kan systemeffekter som hyperkortisisme og binyrebarksuppresjon forekomme. Behandling: Støttende og symptomatisk behandling. Dersom behandlingen må seponeres pga. overdose med formoterol, skal behandling med passende inhalasjonskortikosteroid vurderes. Se Giftinformasjonens anbefalinger for formoterol R03A C13 og glukokortikoider H02A B på www.felleskatalogen.no. **Egenskaper:** For farmakologiske egenskaper, se pkt. 5 i preparatomtalene. **Pakninger og priser: 80 mikrogram/4,5 mikrogram:** 120 doser[2] kr 417,40 (trinnpris 268,60). 3 × 120 doser[2] kr 1179,80 (trinnpris 733,20). **160 mikrogram/4,5 mikrogram:** 120 doser[1] kr 417,40 (trinnpris 285,60). 3 × 120 doser[1] kr 1179,80 (trinnpris 784,30). **320 mikrogram/9 mikrogram:** 60 doser[1] kr 396,60 (trinnpris 280,40). 3 × 60 doser[1] kr 1079,40 (trinnpris 768,70). **Refusjon:** Refusjonsberettiget bruk: [1]Regelmessig behandling av bronkialastma når det er behov for en kombinasjon av langtidsvirkende beta-agonist og inhalasjonssteroid for pasienter hvor inhalasjonssteroid og korttidsvirkende $beta_2$-agonister ikke gir tilstrekkelig kontroll av sykdommen samt for pasienter hvor inhalasjonssteroid kombinert med langtidsvirkende $beta_2$ agonist allerede gir tilstrekkelig kontroll av sykdommen. Refusjon ytes kun til pasienter med moderat og alvorlig KOLS (FEV1 < 60% av forventet verdi). Refusjonskode:

ICPC		Vilkår nr
R95	Kronisk obstruktiv lungesykdom	90
R96	Astma	92

ICD		Vilkår nr
J44	Annen kronisk obstruktiv lungesykdom	90
J45	Astma	92

Vilkår: (90) Refusjon ytes kun til pasienter med etablert KOLS. - Diagnosen må være verifisert ved spirometri. - Hvis spirometri ikke kan gjennomføres, må årsaken journalføres. (92) Diagnosen astma må være verifisert ved hjelp av spirometri hos barn over 8 år og voksne. Hvis spirometri ikke kan gjennomføres, må årsaken journalføres.

[2]Regelmessig behandling av bronkialastma når det er behov for en kombinasjon av langtidsvirkende $beta_2$-agonist og inhalasjonssteroid: - for pasienter hvor inhalasjonssteroid og korttidsvirkende $beta_2$-agonist ikke gir tilstrekkelig kontroll av sykdommen - for pasienter hvor inhalasjonssteroid kombinert med langtidsvirkende $beta_2$-agonist allerede gir tilstrekkelig kontroll av sykdommen. Cystisk fibrose.

ICPC		Vilkår nr
R96	Astma	92
T99	Cystisk fibrose	-

ICD		Vilkår nr
E84	Cystisk fibrose	-
J45	Astma	92

Vilkår: (92) Diagnosen astma må være verifisert ved hjelp av spirometri hos barn over 8 år og voksne. Hvis spirometri ikke kan gjennomføres, må årsaken journalføres.

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ARTICLE OPEN

Check for updates

Care by general practitioners for patients with asthma or COPD during the COVID-19 pandemic

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The impact of the COVID-19 pandemic on general practitioners' (GP) care for patients with asthma and/or COPD is largely unknown. To describe the impact of the pandemic on asthma or COPD-related GP care, we analysed routinely recorded electronic health records data from Dutch general practices and out-of-hours (OOH) services. During the COVID-19 pandemic (2020), the contact rates for asthma and/or COPD were significantly lower in GP practices and OOH services compared with the pre-pandemic period (2019) (respectively, 15% lower and 28% lower). The proportion of telephone contacts increased significantly with 13%-point in GP practices and 12%-point at OOH services, while the proportion of face-to-face contacts decreased. Furthermore, the proportion of high urgent contacts with OOH services decreased by 8.5%-point. To conclude, the overall contact rates in GP practices and OOH services decreased, while more contacts were remote. Lower contact rates have, after a short follow-up, not resulted in more patients with exacerbations in OOH care. However, this might still be expected after a longer follow-up.

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INTRODUCTION

The COVID-19 pandemic has had an enormous impact on public health and health care. In the first year of the pandemic, there were ~5 million reported infections and ~90,000 COVID-related reported deaths worldwide, of which 1.7 million and 35,000 were in Europe[1]. However, not everyone is equally affected by the COVID-19 pandemic[2]. Particularly, patients with (chronic) comorbidity were more likely to have a more severe course of their disease from a COVID-19 infection[3–6]. This may lead, for example for patients with asthma or Chronic Obstructive Pulmonary Disease (COPD), to more exacerbations and structural damage in the lungs, worsening their respiratory condition[7]. Measures to prevent the spread of the virus also affected these patients indirectly, as regular care with their general practitioner (GP), including disease management programmes for chronically ill patients, were postponed (e.g. lung function tests and consultations) or provided remotely (e.g. by telephone, video or e-consult)[8–12]. Furthermore, many chronically ill patients did not visit their GP during the COVID-19 pandemic because they were afraid of becoming infected with SARS-CoV-2[13].

In the Netherlands, GPs are the first point of contact for patients and are the gatekeepers to specialised secondary care[14] (Box 1). In addition, GPs and practice nurses (a nurse who works in a GP office) play an important role in the care and management of patients with chronic diseases, such as asthma or COPD[14]. In 2020, ~1.1 million Dutch people (of a total population of ~17.4 million) had asthma and/or COPD[15,16]. These patients consult their GP and practice nurse regularly as part of disease management programmes e.g. to assess their burden of illness and discuss lifestyle and (inhaled) medication. Furthermore, the GP can refer patients to other healthcare providers if indicated[17]. Regular check-ups and consultations are meant to reduce symptoms and prevent exacerbations[18–20]. As a consequence, when this regular care is suspended, postponed, or avoided, patients are expected to have more exacerbations of their condition, needing immediate care, including out-of-hours. Therefore, OOH services and other emergency care providers act as a safety net throughout the health system and can be an indicator of problems caused by changes elsewhere in the health system[21,22].

The COVID-19 pandemic and associated measures may both have had an impact on the healthcare use of patients with asthma and/or COPD. However, it is unclear what the impact is of the COVID-19 pandemic on asthma and/or COPD-related care. Therefore, this study aimed to describe the impact of the COVID-19 pandemic on asthma or COPD-related care from GP practices and OOH services. We aimed to answer the following research questions: (1) How did contact rates for patients with asthma and COPD in GP practices and OOH services differ during various phases of the COVID-19 pandemic compared to 2019? (2) How did these contacts take place during the phases of the COVID-19 pandemic compared to 2019? and (3) To what extent did the urgency of asthma and COPD contacts at the OOH services change during the COVID-19 pandemic compared to 2019?

RESULTS

Table 1 provides an overview of the characteristics of the patient populations with contact(s) for asthma and/or COPD in GP practices (during office hours) and at OOH services.

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Box 1. General practice care in the Netherlands

General practitioners (GPs) are the first point of contact for patients with a healthcare professional. Dutch GPs are the gatekeepers for specialised secondary care (referral system)[14] and virtually every citizen is listed as a patient in a specific practice (list system). During office hours, GP care is provided in local general practices with one or more GPs and practice nurses. Outside office hours, GP care is provided in regional out-of-hours (OOH) services in central locations (often in conjunction with a hospital) populated by GPs and triagists who assess levels of urgency and determine the follow-up action.

General practices

GPs assess patients' physical and mental symptoms, problems, and urgency, taking into account the medical history, and preferences of the patient[14]. Together with the patient, GPs determine which care is necessary and provide this care or refer to other healthcare professionals. GPs are also responsible for preventative care of chronic patients (diabetes, COPD, and cardiovascular risk management) to avert complications. In addition, they provide preventive care for mental health problems and older adults to support physical, cognitive, and psychological frailty[14]. In GP practices, most contacts are face-to-face.

Out-of-hours services

During the evening, nights, and weekends, OOH services provide urgent medical care, which must be evaluated immediately or within a few hours[14]. Prior to a contact with the OOH service, patients should first call the OOH services, where the telephone triagist assesses the level of urgency based on the severity of the complaints stated by the patient (U0 loss of vital functions – U5 no chance of harm)[47]. The level of urgency determines how quickly a patient will receive care and whether this will be through telephone contact, contact at the OOH service location, or via home visit[47].

Table 1. Characteristics of the patient populations in the databases for GP practices and OOH services.

	GP practices		OOH services	
	2019	2020	2019	2020
Number of patients (with at least one contact) per 1000 registered patients/inhabitants of catchment area				
Asthma	26.9	23.0	1.1	0.8
COPD	16.0	13.8	0.9	0.7
Number of contacts per 1000 registered patients/inhabitants of catchment area				
Asthma	68.6	57.3	1.2	0.9
COPD	59.8	50.9	1.2	0.9
Sex in %				
Male	44.4	43.5	46.2	46.7
Female	55.6	56.5	53.8	53.3
Age in %				
0–4 years	1.6	1.0	8.5	5.1
5–17 years	6.5	5.6	9.5	10.1
18–44 years	19.4	20.7	19.0	22.0
45–69 years	45.5	45.3	31.7	32.6
70 years and older	27.0	27.4	31.3	30.2

Contact rates for asthma or COPD in 2020 (during the COVID-19 pandemic) compared to 2019

The overall contact rates for asthma or COPD-related care in general practices and at OOH services were lower in 2020 (during the COVID-19 pandemic) compared to 2019. In 2019, there were 127.9 contacts for asthma or COPD per 1000 registered patients in GP practices, compared to 108.6 contacts per 1000 in 2020 (Table 1). This represents a decrease of 15%. After an initial increase in contacts for asthma or COPD in GP practices at the start of the pandemic (weeks 9–13), contact rates decreased considerably, resulting in a lower contact rate during phase 1 in 2020, than in the same period in 2019 (Fig. 1 and Table 2). However, due to the fluctuation in this period, phase 1 did not significantly differ from the same period in 2019 ($p = 0.081$). In the second and third phases of the COVID-19 pandemic, the contact rates in GP practices were significantly lower in 2020 than in 2019 (resp. $p = 0.001$ and $p < 0.001$).

In 2019, there were 2.5 contacts per 1000 inhabitants of the catchment area for asthma and/or COPD with OOH services, compared to 1.8 contacts per 1000 in 2020 (Table 1). This represents a decrease of 28%. During the first wave of the COVID-19 pandemic, there was a steep increase in contacts for asthma or COPD with OOH services between weeks 11 and 14 (Fig. 1). After this initial increase, contact rates in phase 1 decreased considerably and remained lowered. Due to this fluctuation, phase 1 did not significantly differ from the same period in 2019 ($p = 0.127$) (Table 2). During phases 2 and 3, the contact rates were significantly lower in 2020 for asthma/COPD, than in the same periods in 2019 at OOH services (both $p < 0.001$).

Type of contact for asthma or COPD in 2020 (during the COVID-19 pandemic) compared to 2019

During the COVID-19 pandemic, there was a shift from face-to-face contacts to telephone contacts for asthma and COPD-related care. The proportion of face-to-face contacts in GP practices significantly decreased from 75% in 2019 to 63% in 2020 (all phases $p < 0.001$), while the proportion of telephone contacts significantly increased from 17% in 2019 to 30% in 2020 (all phases $p < 0.001$), see Fig. 2 and Table 2. The decrease in the proportion of face-to-face contacts and the increase in the proportion of telephone contacts was initiated in phase 1 and partly reversed in the following phases (Fig. 2). The proportion of home visits decreased from 8% in 2019 to 6% in 2020, with a significant decrease in phases 1 ($p = 0.003$) and 3 ($p < 0.001$) during the pandemic, compared to 2019 (Table 2).

The proportion of face-to-face contacts at OOH services decreased significantly from 51% in 2019 to 40% in 2020 (phase 0: $p = 0.066$, phases 1–3: $p < 0.001$), while the proportion of telephone contacts significantly increased from 21% in 2019 to 33% in 2020 (phase 0: $p = 0.032$, phases 1–3: $p < 0.001$), see Fig. 3 and Table 2. The proportion of home visits did not change significantly in 2020 compared to 2019.

Changes in the type of contact for asthma or COPD during the various phases of the COVID-19 pandemic

When comparing the various phases in 2020 (during the COVID-19 pandemic) in GP practices, the proportion of face-to-face contacts was significantly lower in phase 1 compared to phase 0, while the proportion of telephone contacts was significantly higher (both $p < 0.001$), see Fig. 2 and Table 3. However, the proportion of telephone contacts again became significantly lower in phase 2 compared to phase 1, while face-to-face contacts became significantly higher (respectively, $p = 0.028$ and $p = 0.015$). During the COVID-19 pandemic, the proportion of home visits only decreased significantly in phase 1 compared to phase 0 ($p < 0.001$), see Table 3.

For OOH services, the proportion of telephone contacts significantly increased ($p < 0.001$), while the proportion of face-to-face contacts and the proportion of home visits significantly decreased (respectively, $p = 0.001$ and $p < 0.001$) in phase 1 of the COVID-19 pandemic, compared to phase 0. In phases 2 and 3 of the pandemic, there were no significant changes in the proportions of the different types of care (between phases 1–2 and 2–3) (Table 3).

Allocation of urgency levels at OOH services

During the COVID-19 pandemic, higher urgency levels were assigned less often to patients who contacted the OOH service for asthma or COPD (Table 4). In 2020, U2 and U3 (very urgent) were assigned less often, compared to 2019, respectively 9.7 to 5.6 per

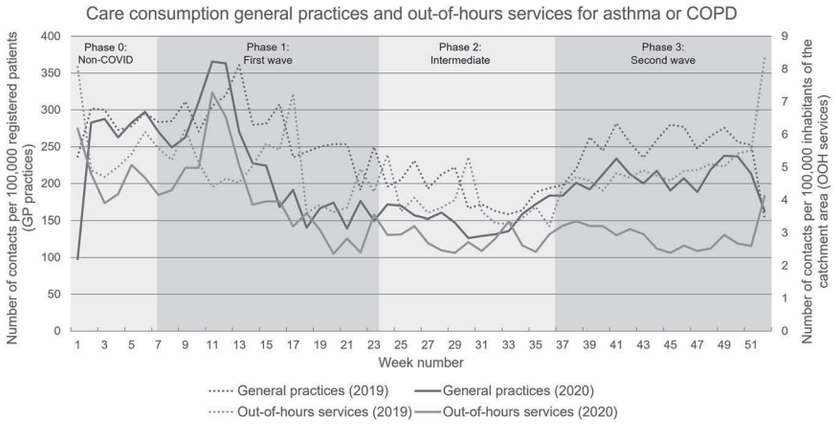

Fig. 1 The contact rates for asthma or COPD in general practices and out-of-hours services. The contact rates for asthma or COPD in general practices (blue) and out-of-hours services (orange), for 2019 (dots) and 2020 (lines).

1000 inhabitants of the catchment area (U2) and 6.2 to 4.6 per 1000 (U3). In contrast, the low urgency (U4 and U5) hardly changed. When looking at the proportional distribution, the urgency level of U2 decreased significantly in 2020 by 8.5%-point, while U4 and U5 significantly increased by 2.6%-point and 5.9%-point respectively (all $p < 0.001$).

Post hoc analyses

To investigate whether there were differences in contact rates between patients with asthma or COPD, we analysed these separately in a sensitivity analysis for both GP practices and OOH services. No major differences between the two conditions were found. Contact rates in GP practices for patients with asthma decreased by 16.5% in 2020 compared to a decrease of 14.9% for COPD (Table 1). Contact rates with OOH services decreased by 25% for both asthma and COPD (Table 1). In addition, for phases 1, 2, and 3, results were overall similar for asthma and COPD. However, there were some baseline differences (phase 0) between conditions as patients with COPD in GP practices showed a borderline significant decrease ($p = 0.050$) in 2020 vs. 2019 compared to patients with asthma ($p = 0.507$). In OOH services, patients with asthma showed a significant decrease ($p = 0.013$) in 2020 vs. 2019, while COPD did not ($p = 0.073$). As our analyses focused on phases 1, 2 and 3 of the COVID-19 pandemic, this baselined difference was considered not to be relevant, justifying our approach to analyse the two diseases together.

We also performed analyses of the proportional difference in contact rates in 2020 compared to 2019 for different age categories (0–17 years, 18–69 years, 70 years and older). COPD was not included in the analyses for 0–17 years for GP practices and OOH services, because there were no contacts for that age group for COPD. During the start of the COVID-19 pandemic (weeks 9–13) in 2020 compared to 2019, there was an increase in contact rates with GP practices for all age groups, after which contact rates declined for all age groups (from week 13 onwards), see Fig. 1 in Supplementary File. However, for asthma, we observed a greater decrease in contacts for patients aged 0–17 years in GP practices. For OOH services, there was also an increase in contact rates during the start of the COVID-19 pandemic (weeks 10–14) in 2020 compared to 2019, however, only for patients aged 0–17 years and 18–69 years, see Fig. 2 in Supplementary File.

DISCUSSION

This study showed the impact of the COVID-19 pandemic on general practitioner care for patients with asthma and COPD, both in GP practices (during office hours) and at OOH services, in terms of contact rates, how the care was provided, and the urgency levels of contacts with OOH services. Both in GP practices and at OOH services, contact rates for asthma or COPD decreased during the COVID-19 pandemic. In addition, more care was provided by telephone. In OOH services, the proportion of telephone contacts remained at an increased level during all phases of the COVID-19 pandemic, while in GP practices, the proportion decreased again during a later phase of the pandemic. Furthermore, during the pandemic, higher urgency levels were less often assigned to patients for contacts with OOH services for asthma or COPD.

From the start of the COVID-19 pandemic, a considerable decrease in contact rates for asthma or COPD was observed in GP practices and OOH services. Firstly, the decrease in contact rates in GP practices was likely initiated by the recommendations of 'The Dutch College of General Practitioners' (NHG) to delay routine care for patients with asthma or COPD and to suspend regular lung function tests (spirometry). The reduction in chronic care contacts was also observed in Belgium[23]. Secondly, reduced contact rates in both GP practices and OOH services may be explained by fewer exacerbations, as was found by Shah et al.[7] for asthma patients[7]. The presentation of fewer exacerbations in asthma and COPD patients in both GP practices and OOH services may be related to a decreased circulation of respiratory viruses due to the containment measurements (i.e. social distancing, face masks)[7,24] and a decrease in air pollution, due to less traffic[25–27]. Thirdly, some patients did not consider their complaints serious enough to make an appointment with their GP, and for other patients, doctors' assistants have considered this. Patients' decisions were also influenced by media reports of overcrowded healthcare facilities and they thought that it was not even possible to make an appointment with their GP[28]. Last, it is possible that patients with asthma or COPD improved their self-management skills, due to concerns about getting infected with SARS-CoV-2 when visiting a GP, resulting in a decreased need for care[24,26]. However, it remains unclear to what extent each of the above reasons played a role in the reduction of contact rates in both GP practices and OOH services.

During the COVID-19 pandemic, we observed a relative increase in telephone contacts and a decrease in face-to-face contacts for asthma or COPD-related GP care, which was in line with previous studies[9,13,29]. After the first wave of COVID-19 infections, the proportion of telephone contacts remained heightened in OOH services, while GP practices increased their face-to-face contacts. A possible explanation could be that GPs in GP practices wished to see their patients face-to-face again. In contrast, GPs in OOH services became accustomed to providing care remotely (i.e., telephone contacts). Furthermore, the transition to remote care at OOH services may have resulted in more efficient care and less

Table 2. Mean and standard deviation for the contact rates, the proportion of the type of contact (2019 and 2020), and differences in contact rates and the type of contact between 2019 and 2020 presented per phase of the COVID-19 pandemic, both for GP practices and OOH services.

	2019	2020	Difference between 2019 and 2020			
	Mean (SD)	Mean (SD)	Coefficient	95% CI		*p* value
GP practices contacts per 100,000 registered patients						
Phase 0	281.7 (21.1)	253.8 (64.8)	−28.0	−72.6	16.7	0.220
Phase 1	269.4 (45.0)	218.9 (75.3)	−50.5	−107.2	6.2	0.081
Phase 2	189.7 (23.9)	154.4 (19.7)	−35.3	−56.5	−14.2	0.001
Phase 3	251.0 (32.3)	208.4 (20.4)	−42.6	−62.7	−22.5	<0.001
OOH services contacts per 100,000 inhabitants of the catchment area						
Phase 0	5.6 (1.1)	4.7 (0.7)	−1.0	−1.8	−0.1	0.031
Phase 1	4.9 (1.0)	4.0 (1.4)	−0.8	−1.9	0.2	0.127
Phase 2	3.8 (0.6)	2.8 (0.3)	−1.0	−1.4	−0.6	<0.001
Phase 3	5.1 (0.9)	2.9 (0.4)	−2.1	−2.7	−1.6	<0.001
The proportion of the type of contact in GP practices[a]	% (SD)	% (SD)	Coefficient	95% CI		*p* value
Face-to-face contact						
Phase 0	75.4% (0.7%)	73.0% (0.9%)	−0.1	−0.2	−0.1	<0.001
Phase 1	75.4% (2.1%)	57.5% (7.6%)	−0.8	−1.0	−0.6	<0.001
Phase 2	75.0% (1.2%)	62.1% (2.5%)	−0.6	−0.7	−0.5	<0.001
Phase 3	75.3% (1.3%)	63.2% (3.4%)	−0.6	−0.7	−0.5	<0.001
Telephone contact						
Phase 0	15.7% (9.4%)	17.7% (1.4%)	0.1	0.1	0.2	<0.001
Phase 1	16.7% (1.6%)	36.3% (9.2%)	1.0	0.8	1.3	<0.001
Phase 2	17.4% (1.2%)	30.0% (3.2%)	0.7	0.6	0.8	<0.001
Phase 3	16.3% (1.3%)	30.5% (3.0%)	0.8	0.7	0.9	<0.001
Home visits						
Phase 0	8.7% (1.0%)	8.9% (1.3%)	0.1	−0.1	0.2	0.649
Phase 1	7.7% (1.2%)	5.4% (1.9%)	−0.4	−0.6	−0.1	0.003
Phase 2	7.4% (1.2%)	7.3% (1.7%)	−0.1	−0.2	0.2	0.933
Phase 3	8.0% (1.3%)	5.7% (0.8%)	−0.4	−0.5	−0.2	<0.001
The proportion of the type of contact in OOH services						
Face-to-face contact						
Phase 0	48.8% (1.2%)	47.4% (2.0%)	−0.1	−0.1	0.1	0.066
Phase 1	51.1% (3.1%)	39.0% (6.3%)	−0.5	−0.6	−0.3	<0.001
Phase 2	48.8% (3.7%)	40.2% (4.7%)	−0.3	−0.5	−0.2	<0.001
Phase 3	52.7% (2.5%)	37.8% (4.5%)	−0.6	−0.7	−0.5	<0.001
Telephone contact						
Phase 0	18.7% (1.1%)	19.9% (0.9%)	0.1	0.1	0.1	0.032
Phase 1	21.0% (2.8%)	35.4% (6.3%)	0.7	0.5	0.9	<0.001
Phase 2	23.8% (3.0%)	34.5% (3.5%)	0.5	0.4	0.7	<0.001
Phase 3	20.1% (2.0%)	35.8% (2.1%)	0.8	0.7	0.9	<0.001
Home visits						
Phase 0	32.5% (1.8%)	32.6% (1.5%)	0.1	−0.1	0.1	0.977
Phase 1	28.0% (3.4%)	25.7% (4.0%)	−0.1	−0.3	0.3	0.124
Phase 2	27.5% (2.8%)	25.3% (3.3%)	−0.1	−0.2	0.1	0.081
Phase 3	27.2% (2.4%)	26.4% (3.5%)	−0.1	−0.2	0.1	0.472

[a]The proportion of the type of contacts in GP practices does not add up to 100%, because digital consultations are not included in this table.

workload and should be considered as a possible solution to the staffing shortages and high workloads in OOH services[30]. Several studies show that remote contacts for respiratory diseases have potential benefits for access to and effectiveness of care when fully integrated with face-to-face contacts[31–34]. A study into the differences between remote and face-to-face check-ups for asthma showed no significant effects with regard to exacerbations or quality of life[35]. This can be a first step towards the integration of remote care for asthma or COPD patients in the Netherlands. However, when implementing this, the lack of non-verbal communication when using remote care should be taken into account[36].

Moreover, in this study, we demonstrated that (face-to-face) care for asthma or COPD in general practices was partially suspended during the COVID-19 pandemic. A possible consequence could be that patients with asthma or COPD are less in

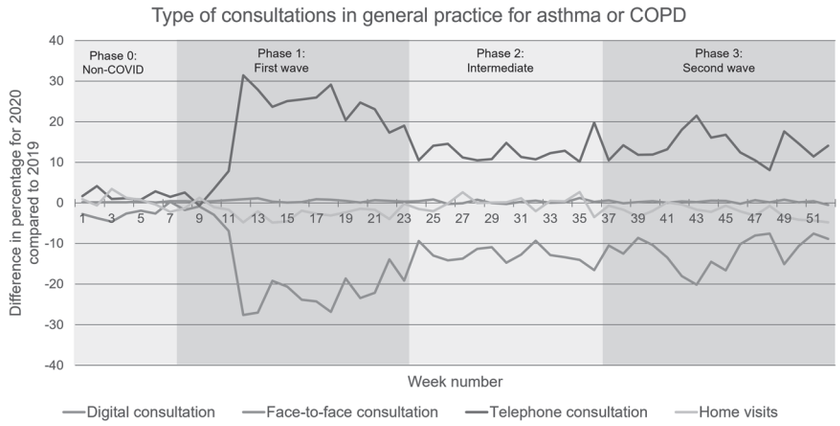

Fig. 2 Type of consultations in general practice for asthma or COPD. The difference in type of consultation in general practice for asthma or COPD, 2020 compared to 2019.

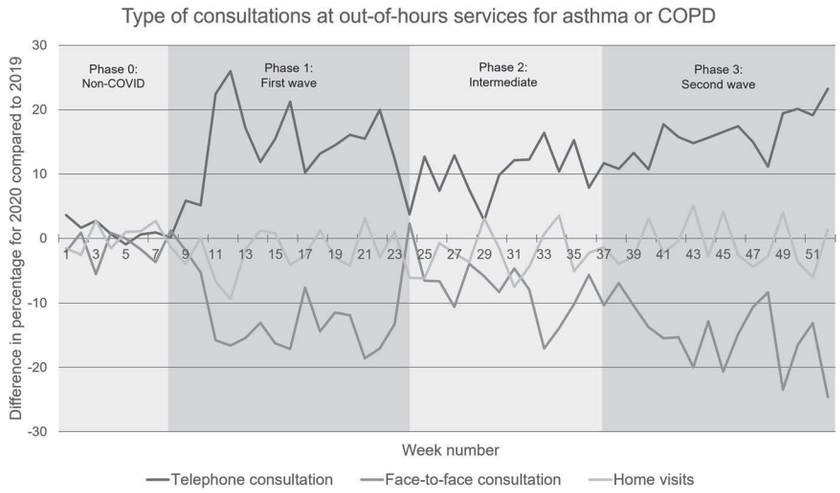

Fig. 3 Type of consultations at out-of-hours services for asthma or COPD. The difference in type of consultation at out-of-hours services for asthma or COPD, 2020 compared to 2019.

control of their disease and, therefore, more likely to contact OOH services in case of acute exacerbations of symptoms, as OOH services are seen as a safety net in the whole healthcare system[21]. However, we observed a decrease in contact rates at both GP practices and OOH services for asthma or COPD during the COVID-19 pandemic. In addition to this, the number of urgent contacts did not increase at OOH services. Based on this study, no short-term adverse effects of postponed chronic care for asthma or COPD were apparent. However, there may be long-term consequences because the expected effect of exacerbations due to postponed care in 2020 will only be visible in 2021 and beyond, indicating the need for continued monitoring. In addition, it is possible that postponed GP care may cause an increase in the need for care in other parts of the (acute) health system (i.e., emergency visits, hospital admissions). Further research is needed to assess the impact of postponed chronic care, involving primary care, secondary care, and mortality statistics, and taking into account multiple chronic diseases of patients. If no consequences are observed, the guidelines for disease management for asthma and COPD patients may be reconsidered.

A strength of our study was the inclusion of both GP practices and OOH services, enabling us to examine the impact of the COVID-19 pandemic on care for asthma or COPD for the entire GP care. Another strength was that we used a large data source (routine healthcare data), which ensures the representativeness of the data. The OOH services database covered 70% of the Dutch population and is, therefore, a representative sample of the whole country. The GP practice database consisted of data from the north, east, and south of the Netherlands. However, two of the included regions are regions in which asthma and COPD are more common[37]. Nevertheless, we examined relative differences, where the large population was helpful. For GP practices, we did not include the western region of the Netherlands and, therefore, we lacked data on the metropolitan area. This could potentially affect the findings. However, a Dutch study of healthcare avoidance by patients at the GP and medical specialists during the COVID-19 pandemic (2020) in the metropolitan area showed similar results, i.e. a decrease of 20.2%[38]. A limitation of this study was that we examined the contact rates separately for GP practices and OOH services so that patient-level statements cannot be made about whether postponed care at GP practices resulted in an increase in contact rates at OOH services. Furthermore, our analyses showed that the number of digital consultations was low and unchanged during the COVID-19 pandemic, while other studies showed that GPs in the Netherlands also intensified digital consultations during the first year of the COVID-19 pandemic[39,40]. This is probably due to reimbursement and/or registration bias in the electronic health records data[41]. The means by which contacts are registered or declared may have distorted the proportion of digital consultations in the results. Based on this, we cannot draw any conclusions

Table 3. Differences between the phases in 2020 for the type of contact, both for GP practices and OOH services.

	F-value	Degrees of freedom	*p* value
Type of contacts GP practices			
Face-to-face contacts			
Phases 0–1	−15.5	51	<0.001
Phases 1–2	5.0		0.028
Phases 2–3	0.6		1.000
Telephone contacts			
Phases 0–1	18.6		<0.001
Phases 1–2	−6.3		0.015
Phases 2–3	0.6		1.000
Home visits			
Phases 0–1	−3.5		<0.001
Phases 1–2	1.5		0.056
Phases 2–3	−1.2		0.312
Type of contacts OOH services			
Face-to-face contacts			
Phases 0–1	−8.5	51	0.001
Phases 1–2	1.4		1.000
Phases 2–3	−3.8		0.296
Telephone contacts			
Phases 0–1	15.5		<0.001
Phases 1–2	−0.9		1.000
Phases 2–3	1.8		1.000
Home visits			
Phases 0–1	−6.9		<0.001
Phases 1–2	−0.5		1.000
Phases 2–3	1.9		0.837

about the extent of digital consultations for asthma/COPD patients in GP care. In addition, the analysis period may have been too short to observe the effects of postponed GP care for asthma or COPD patients, because the need for more (urgent) care, e.g. due to exacerbations, occurred later. Therefore, future studies should focus on patient care pathways with an extended study period to investigate the consequences of postponed care in GP practices, by linking the data of GP practices, OOH services, and secondary care. Finally, it is important to mention that the incidence of asthma and COPD has decreased in 2020 compared to 2019, which may have resulted in fewer patients with asthma or COPD. This may contribute to the fewer contacts we found in 2020.

In conclusion, the care for patients with asthma and COPD by GPs was greatly impacted by the COVID-19 pandemic, resulting in fewer contacts due to postponed chronic care and fewer exacerbations as a side effect of the COVID-19 measures. This also translated into less high urgent contacts for patients with asthma and COPD with the OOH services. Furthermore, there was a shift towards remote care, which has so far been maintained at OOH services and may also be a tool for efficient asthma and COPD care after the pandemic. This study does not yet show negative effects for patients with asthma or COPD, but it is likely that these are still to come, making it necessary to remain vigilant and continue monitoring in a broader setting, including further research on the long-term impact of the COVID-19 pandemic on care for asthma or COPD patients in primary and secondary care.

METHODS

Study design and setting

In this observational study, deidentified, routinely recorded, electronic health records data from general practices and OOH services were used. For general practices (during office hours), data from three electronic health records-based repositories in the Netherlands were used: (1) Academic General Practitioner Development Network (Academische Huisartsen Ontwikkel Netwerk—AHON) with 57 participating practices, (2) Family Medicine Network (FaMe-Net) with 6 participating practices, and (3) Research Network Family Medicine Maastricht (RNFM) with 27 participating practices. These are regional networks covering the north, east, and south of the Netherlands. These databases together have a dynamic patient population of ~420,000 patients from the north, south, and east of the Netherlands.

For the OOH services, data from Nivel Primary Care Database (Nivel-PCD), routinely electronic health records from 30 OOH services were used, representing a joint catchment area of almost 12 million people from the Netherlands (60% of all OOH services, and 70% of the Dutch population). The database is representative for the Dutch population concerning sex, age, and region[42].

Contact rates and their characteristics

The outcome measures of this study were the contact rates for asthma or COPD, defined by (1) the number of all contacts with the GP or practice nurse per 1000 registered patients in GP practices, and (2) the number of all contacts with OOH services per 1000 inhabitants of OOH services' catchment area. Contrary to GP practices' list system, in OOH services there are no patients registered, and therefore, the catchment areas of OOH services were used as the denominator. In both GP practices and OOH services, the diagnoses related to the contacts were recorded routinely with International Classification of Primary Care version 1 (ICPC1 codes). ICPC code R96 was used to identify contacts concerning asthma and R95 for COPD[43–45]. Other outcome measures were the types of contacts and urgency levels (only for OOH services). The types of contacts were derived from reimbursement claims codes and included face-to-face, home visits, and telephone contacts for both GP practices and OOH services, and additionally digital consultation for GP practices. Urgency levels of contacts with OOH services were classified as follows: U0 (resuscitation), U1 (immediate danger to life—immediate care), U2 (threat to vital signs or organ damage—care as soon as possible), U3 (real chance of damage—care within a few hours), U4 (negligible chance of damage—care same day), and U5 (no chance of damage—care next working day).

Phases of COVID-19 pandemic in the Netherlands

The course of the COVID-19 pandemic, in terms of the number of COVID-19 infections and the related containment measures, varied between various phases of the pandemic. To interpret the changes in contact rates, they must be observed in the context of the pandemic in the Netherlands. Therefore, a brief overview of important containment measures and the waves of COVID-19 infections in 2020 in the Netherlands is provided in Table 5[46].

Data analysis

The characteristics of the population, i.e., the number of contacts for asthma/COPD, and the number of patients with a contact for asthma/COPD are described per 1000 registered patients (GP practices) per year and per 1000 inhabitants of the catchment area (OOH services) per year. In addition, sex, and different age groups are described as the proportion of all contacts for asthma and COPD. All analyses were performed separately for GP practices and OOH services. The contact rates were aggregated and

Table 4. The distribution of urgency levels at OOH services for asthma/COPD, displayed per 1000 inhabitants of the catchment area and the proportion of the distribution, for phases 1–3 in 2019 (before the COVID-19 pandemic) and phases 1–3 in 2020 (during the COVID-19 pandemic).

Urgency level[a]	2019 Pre-pandemic		2020 Pandemic		*Z* (*p* value)[b]
	Per 1000 inhabitants of the catchment area	%	Per 1000 inhabitants of the catchment area	%	
U1 (immediate danger to life—immediate care)	0.6	2.9%	0.4	2.6%	−1.81 ($p = 0.070$)
U2 (threat to vital signs or organ damage—care as soon as possible)	9.7	47.2%	5.6	38.7%	−17.97 ($p < 0.001$)
U3 (real chance of damage—care within a few hours)	6.2	29.9%	4.6	30.2%	2.23 ($p = 0.026$)
U4 (negligible chance of damage—care same day)	1.8	8.9%	1.7	11.5%	8.39 ($p < 0.001$)
U5 (no chance of damage—care next working day)	2.3	11.1%	2.4	17.0%	16.65 ($p < 0.001$)

[a]U0 was not assigned and, therefore, excluded from the table.
[b]Differences between 2019 and 2020 (starting phase 1) in the proportion of the different urgency levels.

Table 5. Phases of the COVID-19 pandemic in terms of the containment measures and waves of COVID-19 infections in the Netherlands.

Phases of the COVID-19 pandemic (2020)	Description of containment measures
Phase 0—week 1–8 (non-COVID phase)	- Period before the first COVID-19 infection in the Netherlands.
Phase 1—week 9–24 (phase first wave)	- First wave of COVID-19 infections. - "A lockdown" was introduced (i.e. social distancing, working from home, and the closing of schools, restaurants, museums, sports facilities, and events).
Phase 2—week 25–37 (intermediate phase)	- A calmer period with fewer COVID-19 infections. - The lockdown was abolished, while limited containment measures were retained (i.e. social distancing).
Phase 3—week 38–53 (phase second wave)	- The second wave of COVID-19 infections. - First, a "partial lockdown" was introduced (i.e. social distancing, restaurants closing early, use of facemasks in public spaces, and closing of museums and swimming pools). - Later in this period a "hard lockdown" with extensive containment measures (i.e. closing of schools, non-essential stores, and sports facilities, working from home).

displayed per week for 2019 and 2020. Means and standard deviations were calculated for the contact rates per phase of the COVID-19 pandemic for 2019 and 2020. We performed a sensitivity analysis to investigate whether contact rates should be reported for all registered patients in GP practices or all registered asthma/COPD patients in GP practices. This resulted in no differences, therefore, we described the contacts rate for all registered patients because for OOH services we also plot this against the entire population. Linear regression analysis was performed, with standard errors corrected for autocorrelation of time series (weeks), to investigate the effect of the COVID-19 pandemic (2020) on contact rates for the different phases over time compared to the pre-pandemic period (2019). The types of contacts were shown as the proportional difference between 2020 and 2019 per week. Logistic regressions were performed with standard errors corrected for autocorrelation of time series (weeks), examining the effect of the COVID-19 pandemic on the proportion of the specific types of contacts for the different phases over time between 2019 and 2020. In addition, for the types of contacts, ANOVA with post hoc analyses (Bonferroni) were performed to examine whether there were differences between the phases during the pandemic in 2020. For each urgency level, the number of contacts per 1000 inhabitants of the catchment area and the proportional distribution were calculated. In addition, a two proportions *z*-test was performed to analyse the difference in the urgency levels between phases 1–3 in 2019 and 2020. All analyses were two-tailed and differences were considered statistically significant if the *p* value was lower than 0.05. For the analysis, the software programme STATA was used (version 16.1).

Ethical considerations

Ethical approval for this study was waived by the medical ethics committee of the University Medical Centre Groningen (reference number: 2020/309). The use of electronic health record data is permitted under certain conditions by Dutch law both for the data from the three general practice registration networks and Nivel-PCD. According to this legislation, neither obtaining informed consent from patients nor approval by a medical ethics committee is obligatory for these types of observational studies, containing no directly identifiable patient data (art. 24 GDPR Implementation Act jo art. 9.2 sub j GDPR). For Nivel-PCD, the project has been approved by the relevant governance bodies of Nivel-PCD under no. NZR-00320.087.

Reporting summary

Further information on research design is available in the Nature Research Reporting Summary linked to this article.

DATA AVAILABILITY

The data underlying this article (both for the three general practice registration networks and Nivel-PCD) will be shared at reasonable request to the corresponding author. For Nivel-PCD this follows the governance of the "Nivel Primary Care Database". Data in the "Nivel Primary Care Database" are extracted from the electronic health records of OOH services. The use of the data for research purposes is subject to approval by a committee representing the health professionals who recorded the data in their electronic health records, reviewing proposals on the relevance for, and privacy of, the OOH services and their patients (https://www.nivel.nl/en/nivel-zorgregistraties-eerste-lijn/nivel-primary-care-database).

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AUTHOR CONTRIBUTIONS

All authors (C.J.R., L.R., T.M.H., E.M., J.W.M.M., T.C.o.H., M.Y.B., L.L.P. and R.A.V.) conceived and designed the study. C.J.R., L.R. and E.M. collected and prepared the

data for analysis. C.J.R. and L.R. analysed the data and all authors contributed to the interpretation of the data. C.J.R. and L.R. drafted the manuscript and all authors provided critical revisions and approved the final submitted version.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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