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Minimal access surgery compared with medical management for gastro-oesophageal reflux disease: five year follow-up of a randomised controlled trial (REFLUX)

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EDITORIAL by McCulloch

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STUDY QUESTION What are the long term effectiveness and side effects of laparoscopic fundoplication compared with medical management for chronic gastro-oesophageal reflux disease (GORD)?

SUMMARY ANSWER After five years, laparoscopic fundoplication continued to provide better relief of GORD symptoms without causing persistent side effects.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS
Laparoscopic fundoplication is known to improve short term relief of GORD. Among people who would otherwise require long term medication for GORD, fundoplication produced sustained benefits with the uncommon adverse effects generally observed soon after surgery.

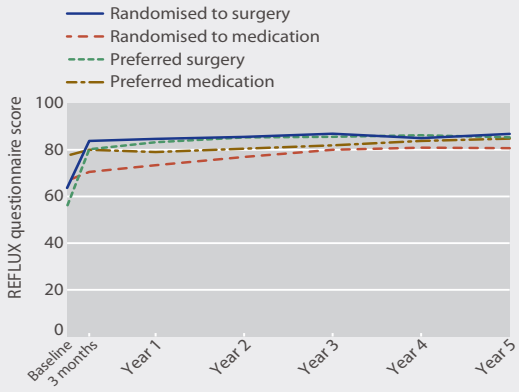
Design

We conducted a five year follow-up of a multicentre pragmatic randomised controlled trial (with parallel non-randomised preference groups) comparing a policy of laparoscopic surgery with a policy of medical management for patients with chronic gastro-oesophageal reflux disease (GORD). There was no subsequent blinding: the surgeon chose the type of fundoplication; after initial optimisation, most medication management was in primary care.

Participants and setting

Participants were respondents to annual postal questionnaires among 810 originally recruited in 21 UK hospitals: 357 were recruited to the randomised comparison (178 randomised to surgery, 179 to medical management) and 453 to the preference groups (261 for surgery, 192 for medical management). All had evidence of GORD and symptoms for >12 months at recruitment. Questionnaire response rates (years 1 to 5) were from 89.5% to 68.9%.

Mean REFLUX questionnaire score* among participants



*Score range 0–100, with higher scores indicating better health related quality of life

Primary outcome

At three and 12 months after surgery and then annually for five years, participants answered the REFLUX questionnaire, a validated measure of health related quality of life for patients with GORD that incorporates assessment of gastrointestinal symptoms and the side effects and complications of both treatments.

Main results and the role of chance

By five years, 63% (112/178) of participants randomised to surgery and 13% (24/179) randomised to medical management had received a fundoplication (with 85% (222/261) and 3% (6/192) of those in the preference groups for surgery and medication respectively). Among responders at five years, 44% (56/127) in the group randomised to surgery and 82% (98/119) of those randomised to medical management were taking antireflux medication.

Differences in the REFLUX score significantly favoured the group randomised to surgery (mean difference 8.5 (95% CI 3.9 to 13.1), P<0.001, at five years) (see figure). SF36 and EQ-5D scores also favoured surgery, but were not statistically significant at five years. The group who expressed a preference for surgery had the worst symptoms at trial entry, but these improved to the level of the group randomised to surgery at follow-up (figure).

Harms

After fundoplication, 3% (12/364) had surgical treatment for a complication, and 4% (16) had subsequent reflux-related operations (most often revision of the fundoplication wrap). From the annual questionnaires, rates of difficulty swallowing, flatulence, and inability to vomit were similar in the two randomised groups.

Bias, confounding, and other reasons for caution

Only 63% of participants randomised to surgery actually underwent fundoplication, reflecting change of mind by patient or surgeon, and 13% of those allocated medical management subsequently had surgery; these rates led to underestimation of differences when judged on analyses adjusted for treatment received.

Generalisability to other populations

These results apply to people requiring long term GORD medication who are fit for surgery. Responders at five years did differ in some respects from non-responders, and this may limit generalisability. The pragmatic design ensured that the clinical policies compared were similar to those that might be applied in normal practice.

Rheumatoid arthritis, anti-tumour necrosis factor therapy, and risk of malignant melanoma: nationwide population based prospective cohort study from Sweden

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Clinical review: Recent advances in the management of rheumatoid arthritis (*BMJ* 2010;341:c6942)

STUDY QUESTION Are people with rheumatoid arthritis at increased risk of malignant melanoma, and does treatment with tumour necrosis factor (TNF) inhibitors increase this risk?

SUMMARY ANSWER Overall, patients with rheumatoid arthritis who have not been treated with biological drugs are not at increased risk of malignant melanomas compared with the general population; patients selected for TNF inhibitor treatment have a 50% higher incidence (an additional 20/100 000 person years) of invasive melanomas than patients not treated with biological drugs.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Recent reports suggest that states of immunosuppression may affect the risk of malignant melanoma and that TNF may be important for the onset and course of melanoma. This study suggests that, overall, rheumatoid arthritis patients treated with TNF inhibitors are at a moderately increased risk of invasive melanoma.

Participants and setting

We identified a nationwide population based cohort, including virtually all adult patients with rheumatoid arthritis alive in Sweden during the study period, through the Swedish outpatient register and a matched general population comparison cohort through the national population register. Data on TNF inhibitor treatment and other covariates came from further register linkages including the Swedish biologics register (ARTIS).

Design, size, and duration

Our main exposures of interest were rheumatoid arthritis and TNF inhibitor treatment. The primary outcome was first ever invasive malignant melanoma. The nationwide rheumatoid arthritis cohort included all patients listed with the disease between 1 January 2001 and 31 December 2010 (n=42 198). Of these, 10 878 started a first TNF inhibitor treatment through 2010. We excluded people with a history of cancer. We used Cox regression to estimate relative risks.

Occurrence and risks of first primary melanoma in 42 198 Swedish RA patients not treated with biological drugs compared with matched general population cohort (n=162 743) and in RA patients (n=10 878) treated with TNF inhibitor compared with patients not treated with biological drugs

	Melanomas/person years				
	Index cohort		Comparator cohort		
Comparison	Non-biological RA	TNF inhibitor RA	General population	Non-biological RA	Relative risk (95% CI)
1	113/203 345	—	393/854 111	—	1.2 (0.9 to 1.5)
2	—	38/57 223	—	113/203 345	1.5 (1.0 to 2.2)

RA=rheumatoid arthritis; TNF=tumour necrosis factor.

Main results and the role of chance

We found 113 melanomas (56/100 000 person years) in the rheumatoid arthritis cohort not treated with biological drugs. Compared with the 393 melanomas (46 per 100 000 person years) observed in the general population comparator cohort, this corresponded to an age and sex adjusted relative risk of 1.2 (95% confidence interval 0.9 to 1.5). During a median 4.8 years of follow-up from start of first TNF inhibitor, 38 invasive melanomas (68/100 000 person years) occurred among rheumatoid arthritis patients who started a first TNF inhibitor treatment. Compared with patients not treated with biological drugs (above), this corresponded to an age and sex adjusted relative risk of 1.6 (1.1 to 2.5), a fully adjusted relative risk of 1.5 (1.0 to 2.2), and a rate difference of approximately 20 per 100 000 person years.

Bias, confounding, and other reasons for caution

We assessed outcome independently of exposure, using prospectively collected data of high completeness. We adjusted for several potential confounders (country of birth, family history of melanoma, educational level, personal history of non-melanoma skin cancer in situ, and several comorbidities), which had little effect on the relative risks. We also investigated accumulated use of methotrexate, duration of rheumatoid arthritis, and presence of rheumatoid factor as predictors of risk of melanoma (which they were not). Nevertheless, because we lacked complete information on accumulated exposures to non-biological rheumatoid arthritis treatment since disease onset, we cannot formally exclude the possibility of residual or unmeasured confounding or of confounding by indication.

Generalisability to other populations

The results are generalisable to other populations with rheumatoid arthritis and similar complexion and exposure to ultraviolet light and immunomodulatory drug treatment. The generalisability to TNF inhibitor treatment in conditions other than rheumatoid arthritis, however, remains unclear.

Study funding/potential competing interests

The Swedish biologics register has agreements with Pfizer, Abbott, Merck, BMS, SOBI, AstraZeneca, and Roche. All decisions regarding the design, performance, and reporting of this study resided in the hands of the authors.

Association between physicians' experience after training and maternal obstetrical outcomes: cohort study

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STUDY QUESTION What is the association between obstetricians' years of experience after training and the maternal complications of their patients during their first 40 years of post-residency practice?

SUMMARY ANSWER Obstetricians' maternal complication rates declined during the first three decades after residency completion, with the improvement being largest in the first decade and diminishing thereafter.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS The notion that physicians' performance improves with experience has intuitive appeal and some empirical support. Among obstetricians practising in Florida and New York, greater number of years of experience was associated with a lower rate of maternal complications over the first 30 years of practice.

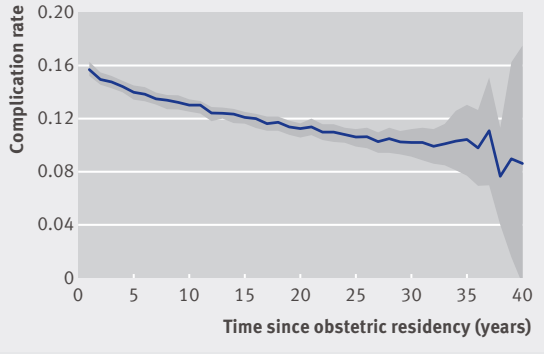
Participants and setting

We analysed data on all obstetric discharges from acute hospitals in Florida and New York between academic years 1992 and 2009.

Design, size, and duration

We conducted a retrospective cohort analysis of 6 704 311 deliveries performed by 5175 obstetricians. We assessed physicians' performance by using a measure of maternal complications that included infection, haemorrhage, and other major operative and thrombotic complications for caesarean deliveries and haemorrhage, severe laceration, infection, and thrombotic complications for vaginal deliveries. We measured outcomes as rates per physician year

Unadjusted annual maternal complication rates by physicians' years of experience



Main results and the role of chance

The figure depicts trends in unadjusted, annual, physician level maternal complication rates for all deliveries based on the full sample of all physicians. Results from regressions in which years of experience were specified as linear splines also indicated that physicians' performance improved over the three decades following training. Based on the sample of all physicians, the adjusted maternal complication rate in the first year after residency was 15.0%. The adjusted maternal complication rate changed by −0.21 (95% confidence interval −0.23 to −0.19) percentage points per year during a physician's first decade of practice, by −0.11 (−0.13 to −0.09) percentage points per year during the second decade, and by −0.05 (−0.08 to −0.01) percentage points per year during the third decade (P<0.001 for second to first decade comparison; P=0.001 for third to second decade comparison). The patterns were comparable for caesarean deliveries and vaginal deliveries and across several sensitivity checks.

Bias, confounding, and other reasons for caution

We used administrative data, which do not capture all differences in severity between patients or a complete range of patients' outcomes. Importantly, we could not observe child related delivery outcomes or assess the potential trade-off between maternal and neonatal outcomes. We also could not follow mothers across multiple deliveries or adjust for parity.

Generalisability to other populations

Generalisability may be limited to obstetricians from Florida and New York.

Study funding/potential competing interests

This research was performed without external financial or material support.

Clinical prediction model to aid emergency doctors managing febrile children at risk of serious bacterial infections: diagnostic study

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- Research: Diagnostic value of laboratory tests in identifying serious infections in febrile children (*BMJ* 2011;342:d3082)
- Research: The accuracy of clinical symptoms and signs for the diagnosis of serious bacterial infection in young febrile children (*BMJ* 2010;340:c1594)

STUDY QUESTION What is the utility of a clinical prediction model to assess the risks of different serious bacterial infections (SBIs) in children with fever at the emergency department?

SUMMARY ANSWER A validated prediction model including clinical signs and C reactive protein was useful for estimating the likelihood of pneumonia and other SBIs in children with fever in an emergency setting.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Clinical signs and symptoms contribute to predicting risks of different SBIs, such as pneumonia and urinary tract infections, each requiring discrete diagnostic and therapeutic management. A validated prediction model integrated clinical signs and C reactive protein to give risk estimates for the presence of both pneumonia and other SBIs, facilitating the targeted management of febrile children.

Participants and setting

Children (1 month to 15 years) with fever at three paediatric emergency care units in the Netherlands (Rotterdam (n=1750) 2003-05, the Hague (n=967) 2007) and the United Kingdom (Coventry (n=487) 2005-06).

Design, size, and duration

In this prospective observational study we developed a clinical prediction model, cross validated it in two Dutch populations, then externally validated it in a UK population. We identified predictors of SBIs from the literature. These were included independent of their statistical contribution, limiting the risk of chance findings. The model, constructed using multivariable polytomous logistic regression analysis, included age, duration of fever, tachycardia, temperature, tachypnoea, ill appearance, chest wall retractions, prolonged capillary refill time (>3 seconds), oxygen saturation <94%, and C reactive protein. We specified three outcome categories (pneumonia, other SBIs, and no SBI), which were defined by bacteriological cultures or clinical consensus. In the derivation populations, 171 children had pneumonia (6%) and 170 had other SBIs (6%); in the validation population 59 children had pneumonia (12%) and 65 had other SBIs (13%).

Main results and the role of chance

Discriminative ability (C statistic) to predict pneumonia was 0.81 (95% confidence interval 0.73 to 0.88); for other SBIs this was 0.86 (0.79 to 0.92). Risk thresholds ≥10% were useful to identify children with SBIs; thresholds <2.5% were useful to rule out SBIs. External validation showed good discrimination for predicting pneumonia (0.81, 95% confidence interval 0.69 to 0.93), discriminative ability for predicting other SBIs was lower (0.69, 0.53 to 0.86).

Bias, confounding, and other reasons for caution

Reference tests were ordered at the doctors' discretion. We used a follow-up period and clinical consensus to minimise the risk of verification bias. Interobserver variability might influence the validity of the model but is inextricably linked to the use of the model by different clinicians in routine practice. We were not able to derive a prediction model for septicaemia or meningitis owing to a limited number of cases. Finally, C reactive protein was measured at the discretion of the doctors. Excluding children without this marker would have selected a subpopulation of children at high risk of SBIs and missing values were imputed.

Generalisability to other populations

We derived and cross validated a prediction model using two large prospective cohorts and assessed validation in a third population from another country. These cohorts lacked uniformity of inclusion criteria, data collection, and outcome measures, reflecting the diversity of clinical practice and reinforcing the model's external validity. A limited number of cases of other SBIs in the external validation population and the large diversity of diagnoses in this group restricted the model's generalisability to other SBIs.

Study funding/potential competing interests

RGN is supported by ZonMW and Erasmus MC Doelmatigheid; RO is supported by an unrestricted grant from Europe Container Terminals and a fellowship grant from the European Society of Paediatric Infectious Diseases in 2010; this report is independent research arising from MT's career development fellowship supported by the National Institute for Health Research. The views expressed are those of the authors and not necessarily those of the National Health Service, National Institute for Health Research, or Department of Health.

Diagnostic performance measures at different risk thresholds of final prediction model (derivation population)

Outcomes and risk thresholds	Sensitivity (95% CI)	Specificity (95% CI)	Likelihood ratio (95% CI)	
			Positive	Negative
Pneumonia:				
≥2.5%	0.90 (0.85 to 0.96)	0.40 (0.36 to 0.45)	1.51 (1.38 to 1.65)	0.24 (0.14 to 0.40)
≥5%	0.78 (0.71 to 0.86)	0.64 (0.61 to 0.67)	2.18 (1.96 to 2.44)	0.33 (0.24 to 0.46)
≥10%	0.60 (0.50 to 0.71)	0.84 (0.82 to 0.85)	3.73 (3.08 to 4.51)	0.47 (0.37 to 0.60)
≥15%	0.47 (0.37 to 0.56)	0.92 (0.90 to 0.93)	5.58 (4.31 to 7.23)	0.58 (0.48 to 0.70)
≥30%	0.16 (0.10 to 0.22)	0.99 (0.98 to 0.99)	11.07 (6.57 to 18.66)	0.85 (0.79 to 0.92)
Other serious bacterial infections:				
≥2.5%	0.90 (0.84 to 0.96)	0.56 (0.53 to 0.60)	2.06 (1.87 to 2.26)	0.18 (0.11 to 0.30)
≥5%	0.82 (0.74 to 0.89)	0.72 (0.70 to 0.74)	2.92 (2.60 to 3.27)	0.26 (0.18 to 0.36)
≥10%	0.70 (0.61 to 0.79)	0.85 (0.84 to 0.87)	4.84 (4.10 to 5.71)	0.35 (0.26 to 0.46)
≥15%	0.55 (0.46 to 0.64)	0.91 (0.90 to 0.93)	6.35 (5.16 to 7.82)	0.49 (0.40 to 0.60)
≥30%	0.19 (0.12 to 0.26)	0.98 (0.97 to 0.99)	9.12 (5.54 to 15.01)	0.83 (0.76 to 0.91)