

# Splenectomy sequelae: an analysis of infectious outcomes among adults in Victoria

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MJA 2012; 196: 582–586  
doi: 10.5694/mja11.10909

Splenectomy, or partial or complete removal of the spleen, has been known to confer a long-term increased risk of infection since 1919.<sup>1</sup> The most feared complication is overwhelming postsplenectomy infection, a bloodstream infection, usually due to pneumococcus, with a 50% mortality rate.<sup>2</sup> Despite an extensive literature on postsplenectomy infection, it remains difficult for clinicians to provide an individualised assessment of that risk for an asplenic patient at the bedside. Since postsplenectomy infections are relatively rare events, large patient populations are needed to estimate incidence reliably. Furthermore, the relatively short follow-up used in many studies may underestimate the frequency of infections. Although most infections occur within the first 2 years after splenectomy, up to a third may be manifested at least 5 years later.<sup>3</sup> In addition, the frequency and types of infections other than post-splenectomy infection, pneumococcal disease and meningitis are poorly documented.<sup>4</sup> The aim of this study was to determine outcomes after splenectomy by studying a group of patients who underwent splenectomy over an 8-year period.

## Methods

About 300 splenectomies are performed each year in Victoria, Australia, which had a population of about 5 million during the study period.

### Data collection

All patients who underwent a splenectomy in Victoria from 1 July 1998 to 31 December 2006 were identified using linked hospital discharges from the Victorian Admitted Episodes Dataset and death registration data.

The Victorian Admitted Episodes Dataset is maintained by the Victorian Department of Health and is based on hospital data compiled by all public

## Abstract

**Objective:** To determine the risk and timing of a broad range of infective outcomes and mortality after splenectomy.

**Design, setting and participants:** Analysis of a non-identifiable linked hospital discharge administrative dataset for splenectomy cases between July 1998 and December 2006 in Victoria, Australia.

**Main outcome measures:** Age, sex, indication for splenectomy, infectious events and death. Patients splenectomised for trauma were compared with patients splenectomised for other indications. Infectious risk was established using Cox proportional hazards models.

**Results:** A total of 2574 patients underwent splenectomy (with 8648 person-years follow-up). Paediatric cases were excluded, leaving 2472 adult cases for analysis. The most common reasons for splenectomy were trauma (635 [25.7%]) and therapeutic haematological indications (583 [23.6%]). After splenectomy, 644 adult patients (26.0%) had a severe infection, with a rate of 8.0 per 100 person-years (95% CI, 7.2–8.4). The risk of severe infection was highest among patients aged  $\geq 50$  years (1.9 per 100 person-years; 95% CI, 1.6–2.7) and those splenectomised for malignancy (14.2 per 100 person-years; 95% CI, 11.8–17.1). Gram-negative infections represented the most frequent causative organism group, accounting for 698 (51%) of bacterial pathogens. *Staphylococcus aureus* was the second most common causative organism.

**Conclusion:** The incidence of severe infection and all-cause mortality differed according to age and underlying reason for splenectomy, was highest among the elderly and those with malignancy, and was lowest among trauma patients. This highlights the need for targeted prevention programs.

and private hospitals in the state. The dataset contains demographic and clinical information on each episode of patient care, with information coded according to the *International statistical classification of diseases and related health problems, 10th revision, Australian modification (ICD-10-AM)*.<sup>5</sup> Death registration data are compiled by the Victorian Registry of Births, Deaths and Marriages.

There are no unique identifiers in these datasets and as such the linked longitudinal dataset of hospital episodes and death registrations has been developed through a process of sequential deterministic linkage. Data released for research are stripped of any potentially identifying data element and in their place is an encrypted unique personal identification number, which serves to bring together data from the same patient over different years of admission. The analysis data are thus personally non-identifiable.

### Splenectomies

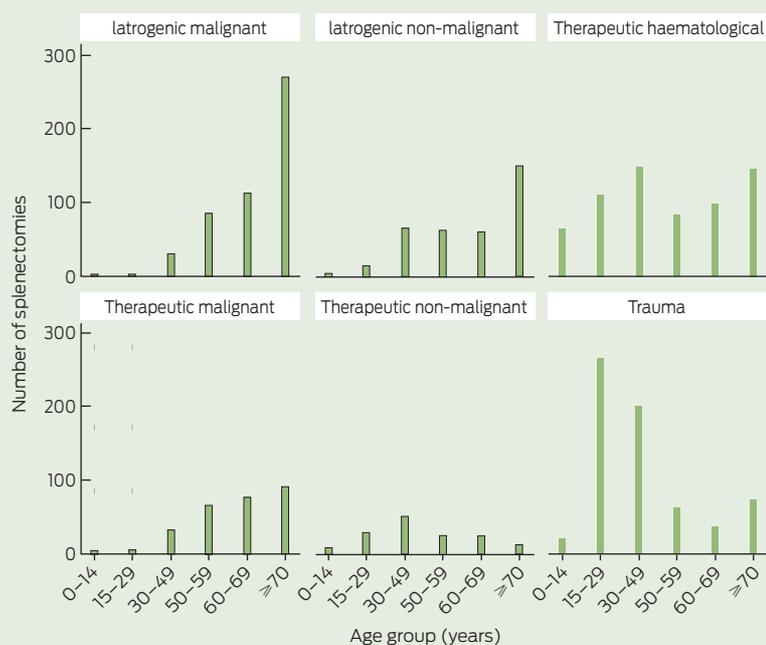
The sampling frame included all patients who underwent splenec-

tomy (defined by the ICD-10-AM procedure codes for splenectomy) between 1998 and 2006. The authors classified the indications for splenectomy into six mutually exclusive groups, with cases having multiple indications ordered hierarchically, regardless of other indications: (i) trauma; (ii) therapeutic malignant (splenectomy performed specifically to manage malignant disease; usually planned); (iii) therapeutic haematological (splenectomy performed specifically to manage haematological disease; usually planned); (iv) therapeutic other (includes treatment of underlying diseases, such as local infections of the spleen or congenital abnormalities of the spleen); (v) iatrogenic malignant (splenectomy performed as an unintended accompaniment to surgery to manage malignant disease; generally unplanned); and (vi) iatrogenic non-malignant (splenectomy performed as an unintended accompaniment to surgery to manage non-malignant disease; generally unplanned).

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Online first 09/05/12

**1 Number of splenectomies, by age group and indication (n = 2574)**



**Infectious outcomes**

Severe infections were defined using ICD-10-AM codes for infections from the hospitalisation data. The authors categorised the codes into groups according to organ system. Those infections occurring in the first 30 days after splenectomy were excluded in order to avoid inclusion of complications potentially resulting from the primary operation or related admission.

**Statistical analysis**

Survival was calculated from the date of splenectomy to either the date of

death or to 31 Dec 2006 for those alive at the end of follow-up.

The time to first severe infection was calculated from the date of splenectomy to the date of the same patient's first admission for an infectious diagnosis. For those without any infections, it was calculated until the end of follow-up.

Incidence rates of first severe infection per 100 person-years and 95% confidence intervals were calculated for sex, age group and indication for splenectomy. Multivariate Cox proportional hazards regression models

were fitted to compute hazard ratios (HRs), adjusted for age, sex and indication for splenectomy. Hazard proportionality was assessed using analysis of scaled Schoenfeld residuals. Paediatric cases were defined as aged less than 15 years at the time of splenectomy.

Survival curves/time to event curves were calculated for time to death, first severe infection and first episode of sepsis by sex, age group and indication for splenectomy.

All reported *P* values are two-tailed and, for each analysis, *P* < 0.05 was considered significant. We used Stata, version 11.0 (StataCorp, College Station, Tex, USA) for all analyses.

The Victorian Department of Health granted ethics approval for this study.

**Results**

A total of 2574 patients underwent splenectomy in Victoria over the 8-year study period from 1 July 1998 to 31 December 2006. There were 8648 person-years follow-up with a mean follow-up of 3 years, 5 months per person. Splenectomised patient demographics are shown in Box 1. There were 102 paediatric cases (<15 years of age). These were excluded from subsequent analysis as not being representative of the overall group, leaving 2472 adult splenectomies for analysis. The most common reasons for splenectomy were trauma (25.7%) and therapeutic haematological indications (23.6%).

**2 Adjusted rates of first severe infection in splenectomised adults (n = 2472)**

	No. of patients	No. of events (%)	Incidence rate <sup>†</sup> (95% CI)	Unadjusted (univariable)		Adjusted (multivariable)*	
				HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>
Men	1325	345 (26.0%)	8.0(7.2–8.9)	1		1	
Women	1147	299 (26.4%)	7.6 (6.8–8.5)	0.9 (0.8–1.1)	0.235	0.8 (0.7–0.9)	0.005
<b>Age</b>							
< 50 years	947	190 (20.1%)	5.1 (4.4–5.8)	1		1	
≥ 50 years	1525	454 (29.8%)	10.1 (9.3–11.1)	2.3 (1.9–2.7)	< 0.001	1.9 (1.6–2.7)	< 0.001
<b>Splenectomy indication</b>							
<b>Therapeutic</b>							
Malignant	269	113 (42.0%)	14.2 (11.8–17.1)	3.5 (2.7–4.6)	< 0.001	2.6 (2.0–3.5)	< 0.001
Haematological	583	176 (30.2%)	8.3 (7.1–9.6)	1.9 (1.5–2.5)	< 0.001	1.8 (1.4–2.4)	< 0.001
Other	138	34 (24.6%)	6.9 (4.9–9.7)	1.6 (1.1–2.4)	0.014	1.6 (1.1–2.4)	0.017
<b>Iatrogenic</b>							
Non-malignant	350	95 (27.1%)	8.0 (6.5–9.8)	1.8 (1.5–2.4)	< 0.001	1.5 (1.1–2.0)	0.011
Malignant	497	123 (24.8%)	9.5 (7.9–11.3)	2.5 (1.9–3.3)	< 0.001	1.8 (1.3–2.4)	< 0.001
Trauma	635	103 (16.2%)	6.9 (4.9–9.7)	1		1	

HR = hazard ratio. \*Proportional hazards test, *P* = 0.2019. † Per 100 person-years.

**3 Site of first severe infection in splenectomised adults (n = 644)**

Site	No. of events (%)	Rate per 100 person-years	95% CI
Respiratory	246 (38.2%)	2.8	2.5–3.2
Sepsis	97 (15.1%)	1.1	0.9–1.4
Skin and soft tissue	66 (10.2%)	0.8	0.6–1.0
Device	47 (7.3%)	0.5	0.4–0.7
Genitourinary	35 (5.4%)	0.4	0.3–0.6
Gastrointestinal	27 (4.2%)	0.3	0.2–0.4
Bone and joint	10 (1.6%)	0.1	0.6–0.2
Central nervous system	3 (0.5%)	0.03	0.01–0.10
Cardiovascular	5 (0.8%)	0.6	0.02–0.10
Uncategorisable	108 (17.0%)	–	–

**Rate of first severe infection**

A total of 644 (26.0%) splenectomised patients had a severe infection requiring hospitalisation with an overall incidence of first severe infection (FSI) of 8.0 per 100 person-years (95% CI, 7.2–8.4).

The rate of FSI differed significantly according to age, sex and indication for splenectomy, with female sex, age < 50 years and trauma as the indication for the splenectomy having significantly lower unadjusted rates of first infection. These relationships did not change after adjustment (Box 2).

The mean incidence rate of FSI in the 12 months after splenectomy from 1998 to 2003 was 7.0 per 100 person-years. Following the introduction of the Victorian Spleen Registry in November 2003, the median incidence rate of FSI for the first 12 months after infection was 6.2 per 100 person-years (P = 0.047).

**Types of infections**

Eighty-three per cent of infections fell into nine categorised body sites; the remainder were uncategorisable (Box 3). Respiratory infections and sepsis (proven or presumed bloodstream infections) were the most common sites of infection. Gram-negative infections represented the most frequent causative organism group, accounting for 698 (51%) of bacterial pathogens. *Staphylococcus aureus* accounted for 414 (31%) of infections. *Streptococcus pneumoniae*, meningococcal species and *Haemophilus influenzae* accounted for 7 (5%), 4 (3%) and 10 (7%) infections, respectively. Compared with splenectomised trauma patients, the adjusted HR of first severe sepsis was 16.5 (95% CI, 6.1–44.6; P ≤ 0.001) for patients splenectomised for therapeutic malignancy; 6.2 (95% CI, 2.4–16.3; P < 0.001) for patients splenectomised for therapeutic

haematological indications; 4.9 (95% CI, 1.7–14.3; P = 0.003) for patients splenectomised for iatrogenic malignancy; and 2.9 (95% CI, 0.7–12.2; P = 0.149) for those splenectomised for therapeutic other indications (Box 4).

**Time to first severe infection after splenectomy**

The rate of FSI after splenectomy declined over time. The highest risk of infection was seen within the first 2 years after splenectomy, with 25% of all FSIs occurring during this time, 50% of infections by 3.7 years, 75% by 5.7 years, and 95% by 7.6 years. The cumulative incidence at 3, 6, 12 and 24 months was 73.4, 53.9, 38.3 and 22.1 per 100 person-years, respectively. However, first infections did continue to occur late, with the cumulative incidence at 8 years being 7.8 per 100 person-years (Box 5).

**Mortality (all-cause)**

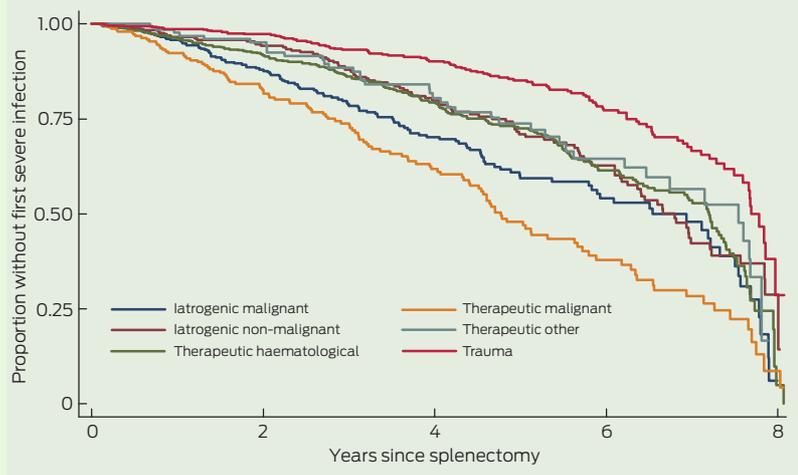
Overall, 562 splenectomised patients (22.7%) died during the follow-up period, with 395 (15.3%) dying within the first 2 years (Box 6). The median survival for patients who died during the follow-up period after splenectomy was 3.1 years (interquartile range [IQR], 1.3–5.3). There was an increased adjusted hazard of death for individuals aged ≥ 50 years compared with those aged < 50 years (HR, 4.8; 95% CI, 3.5–6.3). Women had a decreased hazard of death compared with men (HR, 0.8; 95% CI, 0.6–0.9) (Box 7).

**4 Adjusted rates of sepsis in splenectomised adults (n = 2472)**

	No. of patients	No. of events (%)	Incidence rate <sup>†</sup> (95% CI)	Unadjusted (univariable)		Adjusted (multivariable)*	
				HR (95% CI)	P	HR (95% CI)	P
Men	1325	49 (3.7)	1.1 (0.7–1.5)	1		1	
Women	1147	44 (3.8)	1.1 (0.8–1.5)	1.0 (0.6–1.4)	0.864	0.8 (0.5–1.2)	0.292
<b>Age</b>							
< 50 years	947	23 (2.4)	0.6 (0.4–0.9)	1		1	
≥ 50 years	1525	70 (4.6)	1.6 (1.2–2.0)	2.8 (1.8–4.5)	< 0.001	1.7 (1.0–2.8)	0.063
<b>Splenectomy indication</b>							
Therapeutic							
Malignant	269	33 (12.3)	4.1 (3.0–5.9)	21.1 (8.2–54.0)	< 0.001	16.5 (6.1–44.6)	< 0.001
Haematological	583	29 (5.0)	1.4 (0.9–2.0)	6.5 (2.5–16.8)	< 0.001	6.2 (2.4–16.3)	< 0.001
Other	138	3 (2.2)	0.6 (0.2–1.9)	2.9 (0.8–54.0)	0.144	2.9 (0.7–12.2)	0.149
Iatrogenic							
Non-malignant	350	7 (2.0)	0.6 (0.3–1.2)	2.8 (0.9–8.8)	0.080	2.4 (0.7–7.9)	0.147
Malignant	497	16 (3.2)	1.2 (0.7–2.0)	6.5 (2.4–17.8)	< 0.001	4.9 (1.7–14.3)	0.003
Trauma	635	5 (0.8)	0.2 (0.1–0.5)	1		1	

HR = hazard ratio. \* Proportional hazards test, P = 0.3389. † Per 100 person-years.

### 5 Time to first severe infection after splenectomy, by indication ( $n = 644$ )



Compared with all other reasons for splenectomy, patients who underwent splenectomy for trauma had the lowest mortality. Among patients who died, the median survival for those splenectomised for trauma was 3.7 years (IQR, 1.7–5.8 years), compared with 2.1 years (IQR, 0.8–4.3 years) for iatrogenic malignancy, 3.2 years (IQR, 1.1–5.7 years) for iatrogenic non-malignancy, 3.6 years (IQR, 1.6–5.5 years) for therapeutic haematological indications, 2.6 years (IQR, 0.9–4.6 years) for therapeutic malignancy, and 3.4 (IQR, 1.9–5.5 years) for therapeutic other indications. The adjusted HR of patients undergoing splenectomy for therapeutic malignancy was 2.4 (95% CI, 1.9–3.4;  $P < 0.001$ ) and, for iatrogenic

malignancy, 2.5 (95% CI, 1.7–3.4;  $P < 0.001$ ) (Box 7).

### Discussion

Vaccination, education and antibiotic prophylaxis are recognised as reducing the risk of postsplenectomy sepsis and death.<sup>6</sup> Although the Australasian Society for Infectious Diseases has published guidelines,<sup>7</sup> the appropriate duration of antibiotic prophylaxis in otherwise immunocompetent hosts remains ambiguous. Consequently, the questions remain of who should receive antibiotic prophylaxis and for how long. Committing patients to lifelong antibiotics is difficult; therefore, more information on how to tailor therapy can assist deci-

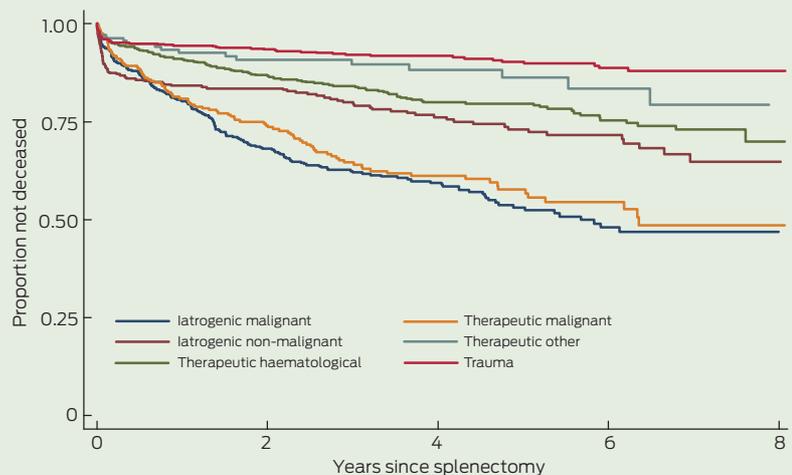
sion making. Our study has identified patient groups at highest risk for adverse outcomes and can be used to guide management decisions.

Based on one of the largest population-based cohorts of splenectomised patients in the literature, our results show that 26% of splenectomised patients had at least one severe infection requiring hospitalisation during the period of observation, with these occurring at a mean of 3.5 years after splenectomy. Our rate of post-splenectomy infection of 8.0 per 100 person years is consistent with international studies (using the same case-definition for severe infection), which have reported rates of 7.0,<sup>8</sup> 7.2,<sup>9</sup> and 7.7<sup>10</sup> per 100 person-years. A Western Australian study reported a substantially lower rate of severe infection of 0.4 per 100 person-years, but included only septicaemia, meningitis and pneumococcal pneumonia.<sup>11</sup> In contrast, a Danish civil registry system reported a risk of severe infection in the community of 2.0 per 100 person-years.<sup>10</sup>

A quarter of severe infections occurred in the first 2 years after splenectomy, with the highest risk in the first 6 months, consistent with the findings in other studies.<sup>8,12–15</sup> A Danish population-based cohort study reported that 10.2% of infections occurred within 90 days of splenectomy, with a relative risk of 18.1 compared with the general population.<sup>10</sup> In our cohort, 31.8% of FSI occurred more than 5 years after splenectomy. Late postsplenectomy sepsis is a less well recognised problem,<sup>11</sup> but fulminant infection has been documented more than 20 years after splenectomy.<sup>11,16,17</sup> Our data support the statement that asplenic patients should be considered to have a risk of developing severe late postsplenectomy infection up to at least 5 years after splenectomy.

The rates of infection were lowest among patients splenectomised for trauma and highest among those splenectomised for malignant disease, in keeping with other literature.<sup>8,9,12,13</sup> Notably, trauma patients may have a partial protective effect from splenosis, owing to self-implanted remnants of the traumatised spleen.<sup>18</sup> Partly because of the problems associated with using an

### 6 Survival after splenectomy, by indication



7 Adjusted (all-cause) mortality rates in splenectomised adults (n = 2472)

	No. of patients	No. of events (%)	Incidence rate† (95% CI)	Unadjusted (univariable)		Adjusted (multivariable)*	
				HR (95% CI)	P	HR (95% CI)	P
Men	1325	313 (23.6)	7.3 (6.5–8.1)	1		1	
Women	1147	249 (21.7)	6.3 (6.0–7.1)	0.9 (0.7–1.0)	0.149	0.8 (0.6–0.9)	0.003
<b>Age</b>							
< 50 years	947	59 (6.2)	1.6 (1.2–2.0)	1		1	
≥ 50 years	1525	503 (33.0)	11.2 (10.3–12.4)	6.5 (5.0–8.6)	< 0.001	4.8 (3.5–6.3)	< 0.001
<b>Splenectomy indication</b>							
Therapeutic							
Malignant	269	101 (37.5)	12.7 (10.4–15.4)	5.0 (4.0–6.9)	< 0.001	2.4 (1.9–3.4)	< 0.001
Haematological	583	112 (19.2)	5.3 (4.4–6.3)	2.2 (1.6–3.1)	< 0.001	2.0 (1.1–2.2)	0.006
Other	138	17 (12.3)	3.4 (2.1–5.5)	1.4 (0.84–2.5)	0.184	1.2 (0.7–2.0)	0.561
Iatrogenic							
Non-malignant	350	86 (24.6)	7.2 (5.9–8.9)	3.0 (2.2–4.7)	< 0.001	1.7 (1.2–2.4)	0.004
Malignant	497	191 (38.4)	14.7 (12.7–16.9)	5.5 (4.1–7.5)	< 0.001	2.5 (1.7–3.4)	< 0.001
Trauma	635	55 (8.7)	2.3 (1.8–3.1)	1		1	

\* Proportional hazards test, P = 0.0803. † Per 100 person-years.

administrative dataset, it is difficult to determine whether infection or death was due to the splenectomised state or to the intrinsic risk conferred by the underlying disease process as well as immunosuppressive therapies. This represents an important limitation of our study.

Late in the period of observation (2003) the Victorian Spleen Registry was established. One of its major roles is in providing education to splenectomised patients.<sup>19</sup> The median incidence of FSI in the first year after splenectomy was higher than in the 4 years before the Registry began, compared with the 2 years after introduction. However, the short follow-up periods make these data difficult to interpret and unlikely to have a major influence over our findings.

Our study found that encapsulated organisms were less common than gram-negative organisms and *S. aureus*. It is difficult to determine if this represents uptake of vaccination and antibiotic prophylaxis in Victoria or a changing pattern of postsplenectomy infections. Targeted studies are warranted to determine the microbiology of infecting organisms and whether penicillin remains the most appropriate agent for antibiotic prophylaxis. Prospective studies are needed to analyse infectious outcome data relating to the use of prophylaxis, both with antibiotics and vaccina-

tions. The use of such data to develop a risk assessment tool, similar to the CHADS<sub>2</sub> score for anticoagulation in atrial fibrillation,<sup>20</sup> and other individualised guidelines for postsplenectomy care would greatly assist clinicians managing asplenic patients.

**Acknowledgement:** Our work was supported by a grant from the Victorian Trauma Foundation.

**Competing interests:** No relevant disclosures.

Received 17 Jul 2011, accepted 19 Mar 2012.

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