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Temporal changes in rates of active management and infant survival following live birth at 22-24 weeks' gestation in Victoria

Running title: Temporal changes in infant survival at 22-24 weeks

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Contributions

RAB designed the study, wrote the ethics, analysed the data, and wrote the draft manuscript. LWD supervised and contributed to the study design, statistical analysis, and edited the manuscript. JLC, MJS and LWD all edited the manuscript. Each author has reviewed the manuscript and approved submission of this version. The authors take full responsibility for the manuscript.

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The authors have no conflicts to declare, real or perceived.

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ABSTRACT

Background
Management of livebirths at 22-24 weeks' gestation in high-income countries varies widely and has changed over time.
Aims
Our aim was to determine how rates of active management and infant survival of livebirths at 22-24 weeks varied with perinatal variables known at birth, and over time in Victoria, Australia.
Materials and methods

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We conducted a population-based cohort study of all 22-24 weeks' gestation livebirths, free of lethal congenital anomalies in 2009-2017. Rates of active management and survival to one year of age were reported. 'Active management' was defined as receiving resuscitation at birth or nursery admission for intensive care.

Results

Over the 9-year period, there were 796 eligible livebirths. Overall, 438 (55%) were actively managed: 5% at 22 weeks, 45% at 23 weeks and 89% at 24 weeks' gestation, but rates of active management did not vary substantially over time. Of livebirths actively managed, 263 (60%) survived to one year: 0% at 22 weeks, 50% at 23 weeks and 66% at 24 weeks. Apart from gestational age, being born in a tertiary perinatal centre and increased size at birth were associated with survival in those actively managed, but sex and plurality were not. Survival rates of actively managed infants rose over time (adjusted odds ratio 1.09 per year, [95% CI 1.01, 1.18], p=0.03).

Conclusions

Although active management rates did not change substantially over time in Victoria, an overall increase in infant survival was observed. With increasing gestational age, rates of active management and infant survival rose rapidly.

Key words:

Periviable birth, resuscitation, extremely preterm, infant survival, infant mortality

MESH terms:

Pregnancy complications, resuscitation, infant mortality, survival

INTRODUCTION

With recent advances in perinatal and neonatal care, the gestational age threshold for providing active management of infants born before 25 weeks' gestation has steadily decreased.[1-3] Neonatal intensive care for infants born at 22-24 weeks' gestation is no longer always considered 'futile', with increasing rates of survival reported in high-income countries with proactive approaches to care of these infants. [4-8]

However, wide variations in approach to management of infants born at 22-24 weeks' gestation are reported, even in high-income countries.[5 9-12] While the United Kingdom, [6, 7] Switzerland, [3, 8] Japan, [13] Germany, [14] and some centres in the United States [15] have been increasingly proactive in their approach to active management of infants born at 22 weeks'

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gestation, others, such as centres in France have a more conservative approach, even at 24 weeks' gestation.[16] Varying recommendations regarding shared decision-making with parents are also reported,[9] with few guidelines clearly defining the 'zone of parental discretion' where parents' preferences for active versus palliative care for births at 22-24 weeks' gestation prevail over the preferences of clinicians. These differences in approach to management of births at 22-24 weeks result in wide variations in outcomes reported within and between countries, especially that of survival.[5]

In 2019, the British Association of Perinatal Medicine (BAPM) published guidelines on the perinatal management of preterm birth before 27 weeks' gestation.[17, 18] They observed that survival in actively treated infants born <27 weeks was influenced by being inborn (born in a hospital with a neonatal intensive care unit), exposure to antenatal corticosteroids, singleton birth, increasing maturity, female sex, and better fetal growth,[18] but these variables may not be predictive in all other regions and at all gestational ages. Moreover, guidelines can become outdated as attitudes to active management and survival rates change over time.

The aim of this study of livebirths at 22-24 weeks' gestation in Victoria, Australia was to determine how rates of active management and survival to one year of age varied with perinatal variables known at birth, particularly gestational age, and year of birth.

MATERIALS AND METHODS

We conducted a prospective population-based cohort study of all livebirths at 22-24 weeks' gestation in Victoria between 1 January 2009 and 31 December 2017. Perinatal data were obtained from the Victorian Perinatal Data Collection (VPDC), at the Clinical Councils Unit, Department of Health and Human Services (DHHS), Victoria. Infant mortality data were obtained from the Consultative Council on Obstetric and Paediatric Mortality and Morbidity (CCOPMM) at DHHS. As per CCOPMM requirements, numerators fewer than five for individual variables were not reported for de-identification purposes.

Ethics

Ethical approval was obtained from the Royal Children's Hospital Human Research Ethics Committee, ID 35160B. Ethics to access VPDC's perinatal data and infant mortality data was approved by CCOPMM , Study IDs RR15-03 and DR18-24.

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Definitions

Gestational age was determined predominately from obstetric ultrasound; otherwise the first day of the last normal menstrual period.

'Active management' was defined as resuscitation interventions at birth, comprising any of positive pressure ventilation via a face mask and/or continuous positive airway pressure in oxygen or air, intubation, chest compressions, administration of adrenaline or volume expanders and/or admission to a neonatal nursery for ongoing intensive care. We ascertained deaths prior to nursery admission despite active resuscitation, and rates of nursery admission for ongoing active management after successful resuscitation at birth. We also determined rates of 'comfort care'/palliative care (no active management) with subsequent death following livebirth.

Inborn birth was defined as birth in a tertiary perinatal centre with a co-located neonatal intensive care unit (NICU), of which there were three in the state, all located in Melbourne. Outborn births comprised the remainder.

Exclusion criteria

Infants born alive following a termination of pregnancy were excluded. Livebirths with lethal congenital anomalies were also excluded as provision of active management would not have altered their outcome.

Birth weight z-scores were computed relative to the British Growth Reference [19] for 23 and 24 week livebirths. For births at 22 weeks' gestation, the data for liveborn males and females from the current dataset were used to calculate z-scores for each sex.

Statistical analysis

Perinatal and infant mortality data were provided to the investigators from the Clinical Councils Unit at DHHS. Data were imported into STATA™ (Version 16.1, StataCorp, College Station, Texas, USA) for analysis.

Gestational age, birthweight z-score, sex, plurality, and inborn birth status were assessed for associations with active management, and with infant survival in actively managed infants.

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Antenatal corticosteroids were not included in the primary analysis because one of the three tertiary centres did not submit these data to the VPDC, because of differences in data reporting systems. Temporal changes in active management rates and in infant survival rates of those actively managed according to year of birth were analysed by logistic regression adjusting for the perinatal variables associated with active management and survival, and reported as adjusted odds ratios (aOR) and 95% confidence intervals (CI). We also assessed temporal changes in active management and infant survival within individual weeks of gestation, and by year of birth.

In a secondary analysis we included antenatal corticosteroid exposure to the model for survival only in those actively managed, because antenatal corticosteroids are strongly associated with offering active management after birth. Because others have reported associations of antenatal corticosteroids with survival in all livebirths in similar gestational age ranges (22-25 weeks),[1, 12, 24, 25] we repeated the analysis with antenatal corticosteroids in all livebirths.

RESULTS

All births at 22-24 weeks' gestation

Over the 9-year period from 2009 to 2017, there were 1,423 potentially eligible births at 22-24 weeks' gestation in Victoria, of which 796 were liveborn (Table 1). With increasing gestational age, liveborn infants were more likely to be inborn, born by caesarean section and have received antenatal corticosteroids (although antenatal corticosteroid data were not available for approximately one-third of the inborn cohort (Table 1). Overall, 554 (70%) liveborn infants were inborn. One infant's birthplace was unknown and coded as missing. Birthweight was missing for four infants. Other perinatal characteristics of the cohort are described in Table 1.

Palliative/comfort care from birth

Overall, 358 (45%) livebirths were not actively managed and died, with rates decreasing with increasing gestational age (Table 2).

Active management

In total, 55% (438/796) of livebirths were actively managed. Resuscitation data were

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available for 434 (99%) actively managed infants (Table 2). An additional four infants did not have resuscitation data available but were admitted to a NICU for ongoing active care and were alive at one year.

Rates of active management rose with increasing gestational age, from 5% at 22 weeks, to 90% at 24 weeks (Table 2). Infants born at 23 weeks' gestation in tertiary perinatal centres (inborn) were more likely to be actively managed compared with non-tertiary (outborn) infants (57% versus 21% respectively). By 24 weeks' gestation, 91% of inborn and 86% of outborn infants were actively managed.

For resuscitation, intubation was the commonest procedure, with chest compressions, adrenaline and volume expanders all used less frequently.

Antenatal corticosteroid data were available for 295/438 (67%) actively managed infants, with 80% exposed to at least one dose. Rates of antenatal corticosteroid exposure rose with increasing gestational age (Table 2).

Twenty-six infants (6%) died before nursery admission despite resuscitation attempts, with the highest proportion of such deaths at 22 weeks (60%) compared with 5% at each of 23 and 24 weeks (Table 2).

In total, 412 infants were admitted to a neonatal nursery for ongoing active care (52% of all livebirths, 94% of actively managed infants).

Temporal changes in active management

Over the nine-year period, there was no substantial change in the overall rate of active management of livebirths at 22-24 weeks' gestation in Victoria, even after adjusting for gestational age, birth weight z-score and inborn birth status (aOR 1.03 per year, [95% CI 0.95, 1.11], p=0.48. Rates of active management at 23 weeks were more variable than at either 22 or 24 weeks (Figure 1A) but did not change substantially over time (aOR 1.08 per year, [95% CI 0.98, 1.20], p=0.13).

There were no differences in rates of birth by caesarean section for all livebirths (p=0.31) or for actively managed infants (p=0.29) over time. There were year-to-year fluctuations in rates

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of exposure to antenatal corticosteroids for all livebirths and in actively managed infants. The highest rates were seen in 2009 and 2011 (91% of actively managed infants) and the lowest in 2013 (73% of actively managed infants).

Deaths in actively managed infants

Of the 438 infants actively managed, 175 (40%) infants died; 25% between 0 to 23 hours, 30% between 24 hours to <7 days (30%), 28% between days 7-27, and 17% between days 28 to 364. No actively managed 22-week infants survived beyond the neonatal period in any year.

Survival rates

Overall, 33% of all livebirths and 60% of actively managed livebirths survived (Table 2). There were no 22-week survivors over the nine-year period (Table 2). Of actively managed infants, 50% at 23 weeks and 66% at 24 weeks survived to one year of age. Of the 56 infants who received chest compressions, 30 (54%) survived, as did 8 of 24 (33%) infants who received adrenaline at birth.

Perinatal variables associated with active management and infant survival

Active management and infant survival were both positively associated with being inborn, increasing gestational age, and increasing birthweight z-score, but not with infant sex or plurality on both univariable and multivariable analysis (Table 3).

Adding antenatal corticosteroids to the model for survival did not change any conclusions about the other variables, and antenatal corticosteroids themselves were not associated with survival in actively managed infants when adjusted for the other variables (OR 1.44, 95% CI 0.71, 2.94, p=0.31). (Supplementary Table 1). However, exposure to antenatal corticosteroids was found to be associated with survival in all livebirths (OR 3.41, 95% CI 1.88, 6.21, p<0.001).

Temporal changes in infant survival of actively managed infants

Survival rates of all actively managed infants rose over time (aOR 1.09 per year, [95% CI 1.01, 1.18], p=0.031), (Figure 1B). In the secondary analysis, the addition of antenatal corticosteroids to the regression model changed the aOR to 1.14 per year (95% CI 1.03,

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1.26), p=0.012. While there were no significant changes in survival rates of actively managed 23-week infants (aOR 0.94 per year, [95% CI 0.82, 1.07], p=0.36), infant survival rates of actively managed 24-week infants increased over time (aOR 1.16 per year, [95% CI 1.05, 1.28], p=0.003).

DISCUSSION

In this contemporaneous population-based cohort study of all livebirths at 22-24 weeks' gestation in the state of Victoria, Australia, rates of active management after birth were low at 22 weeks' gestation but rose quickly with increasing gestational age. Survival to one year of age followed the same trend, with 60% of livebirths who received active management surviving to one year of age overall, but with no survivors at 22 weeks. There were no substantial changes in active management rates over the study period of births from 2009-2017, but we observed a small increase in survival over time, which occurred mostly in 24-week infants. Apart from increasing gestational age, active management and infant survival were both positively associated with being inborn and increased size at birth, but not with infant sex or plurality.

In Victoria, active management and admission to NICU for ongoing intensive care was rare for infants born at 22 weeks compared with rates reported in Northern European population-based cohorts born during similar time periods. In Norway in 2013-2014, 29% (5/17) of all liveborn 22-week infants were intubated at birth and admitted to NICU, and no delivery room deaths of actively managed infants were reported. [11] In Sweden in 2004-2007, 35% (17/49) of all liveborn 22-week infants were admitted to NICU, rising to 52% (50/96) in 2014-2016.[8]

There were no 22-week survivors in 2009-2017 in Victoria. In contrast, in Sweden one-year survival rates of NICU admitted 22-week infants increased over time from 29% in 2004-2007 to 58% in 2014-2016.[8] In the United Kingdom (UK) in 2016, 54% of NICU admitted 22-week infants were alive at one year. [6] Unlike reports from other countries, there has not been an increase in rates of active management or in survival in 22-week infants born in Victoria over the past twenty years.[20] The findings from the current study would suggest that there remains a conservative approach by clinicians to active management at 22 weeks' gestation, consistent with a consensus statement relevant to Australia in 2005.[21]

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In 2015, a scenario-based survey of Australian clinicians' approach to active management of infants born at 23-25 weeks' gestation found the majority of clinicians favoured resuscitating infants born at 24 weeks and "more are considering resuscitation at 23 weeks". [22] Our study provides population-based data from Victoria to substantiate these findings. We demonstrated clinicians in Victoria have a very proactive approach at 24 weeks, with 90% of livebirths actively managed. At 23 weeks, nearly half of all livebirths in Victoria were actively managed and 43% were admitted to NICU.

One-year survival rates of actively managed infants admitted to NICU at 23 weeks did not improve over time in Victoria. Overall, 53% of 23-week NICU admitted infants in Victoria in 2009-2017 survived, compared with 56% in Western Australia in 2004-2010, [23] 45% in the United Kingdom (UK) in 2016, [6] and 66% in Sweden in 2014-2016. [8]

Over the 9-year period, we observed an increase in infant survival rates of actively managed infants, particularly in those born at 24 weeks' gestation who were admitted to NICU in Victoria. Overall, 69% of actively managed, NICU admitted 24-week infants survived to one year in Victoria, compared with 63% in the UK [6], and 79% in Sweden. [8] Survival rates were 81% in NICU-admitted 24-week infants in 2004-2010 in Western Australia. [23]

Given the list of known variables positively associated with survival in recent BAPM guidelines, [17] a surprising observation in our study was that neither infant sex nor plurality were associated with infant survival in all livebirths 22-24 weeks' gestation, or in livebirths offered active management. In a secondary analysis, antenatal corticosteroids were not associated with survival in actively managed infants, but were with all livebirths as the denominator, as has been reported in other studies.[1, 12, 24, 25] The lack of association when the cohort was restricted to just those offered active management may be because we were underpowered relative to some larger cohort studies, and particularly for antenatal corticosteroids because of missing data in one-third of the cohort, but it may also be that sex and plurality (and antenatal corticosteroids) have less influence on survival within such a narrow gestational age range. Most studies reporting positive associations of these variables on survival in infants born extremely preterm have involved wider gestational age ranges than the 22-24 week range of the current study, and also have used all livebirths as the denominator,[12] including previous population-based studies in the state of Victoria.[26]

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Some survivors received chest compressions and/or adrenaline at birth, supporting the viewpoint by Wilkinson et al [27] that advanced resuscitation measures for infants 22-24 weeks' gestation are not always futile.

Study strengths and limitations

The major strength of our study is that it is population-based, spanning a continuous nine-year period of all livebirths and reporting survival data on several different denominators, including livebirths and those who received active management. Moreover, we reported outcomes to one year of age, not just to NICU discharge. Although neonatal intensive care admission and survival rates for cohorts of infants born at 22-24 weeks' gestation (or extremely low birthweight) in Victoria in 1991-1992,[28] 2005,[29] and 2010-2011[30] have been previously reported, the current study reports rates of active management of all livebirths prior to NICU admission, and survival outcomes of these infants, drawn from a longer continuous period over 9 years. We found that survival had increased in the most recent era up to the end of 2017. The major limitations are the relatively small sample size, as discussed above, and the inability to know the true intent concerning active management of births at 22-24 weeks' gestation in Victoria. Because data are reported confidentially, we cannot explore individual births for more details, such as true intents for active management both obstetrically and paediatrically, other than the data provided for this study. A further limitation was the incomplete antenatal corticosteroid data, which were not available for one of the three tertiary centres, because of differences in data reporting systems.

In conclusion, in this study of livebirths in Victoria at 22-24 weeks' gestation in 2009-2017, we found rates of active management and infant survival rose rapidly with increasing gestational age. Although active management rates did not change substantially over time, an overall increase in infant survival was observed, mostly in those born at 24 weeks' gestation.

Table 1: Perinatal characteristics of livebirths 22-24 weeks' gestation 2009-2017

	Gestational age (completed weeks)			
	22 weeks	**23 weeks**	**24 weeks**	**All 22-24**
Livebirths free of lethal anomalies	**N=191**	**N=260**	**N=345**	**N=796**
Maternal Characteristics	N=158	N=215	N=298	N=671

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671 mothers birthed 796 liveborn infants				
Teenage mother <20 years	8 (5%)	10 (5%)	14 (5%)	32 (5%)
Any antepartum haemhorrage	36 (23%)	55 (26%)	96 (32%)	187 (28%)
Hypertensive disorders of pregnancy†	5 (3%)	13 (6%)	14 (5%)	32 (5%)
Spontanous preterm labour	102 (65%)	147 (68%)	199 (67%)	448 (67%)
Caesarean section	7 (4%)	20 (9%)	102 (34%)	129 (19%)
Any antenatal corticosteroids	<5/111 (<4%)	63/140 (45%)	165/204 (81%)	231/455 (51%)
Infants	**N=191**	**N=260**	**N=345**	**N=796**
Inborn	93 (49%)	175 (67%)	286 (83%)‡	554 (70%)‡
Multiple birth	66 (35%)	76 (29%)	87 (25%)	229 (29%)
Male sex	94 (49%)	151 (58%)	186 (54%)	431 (54%)
Birthweight g Mean (SD)	480 (78)	576 (128) ††	666 (101)‡‡	592 (129)§
Birthweight z-score Mean (SD)	0.00 (0.99)	0.13 (1.29) ††	-0.05 (0.82)‡‡	0.02 (1.04)§
Small for gestational age (birth weight z-score <2 SD from mean)	<5 (<2%)	9 (3.5%)††	6 (2%)‡‡	19 (2.4%)§

Data are n (%) unless otherwise specified; †Pre-eclampsia, pregnancy induced hypertension, HELLP syndrome (haemolysis, elevated liver enzymes, low platelets); ‡ One missing birthplace; †† One missing; ‡‡ Three missing; § Four missing

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Table 2: Resuscitation interventions at birth and infant survival of 22-24 week livebirths 2009-2017

	Gestational age (completed weeks)			
RESUSCITATION INTERVENTIONS AT BIRTH	**22 weeks**	**23 weeks**	**24 weeks**	**All 22-24**
Livebirths - n	**191**	**260**	**345**	**796**
Active management – n (% livebirths)	**10 (5%)**	**118 (45%)**	**310 (90%)**	**438 (55%)**
Any resuscitation interventions – n[§]	10	117	307	434
Positive pressure ventilation (PPV) via a mask +/- oxygen	6 (60%)	46 (39%)	133 (43%)	185 (43%)
Continuous positive airway pressure +/- oxygen	<50%[†]	31 (26%)	79 (26%)	113 (26%)
Intubation + PPV	<50%[†]	110 (94%)	262 (85%)	376 (87%)
Chest compressions	5 (50%)	13 (11%)	38 (12%)	56 (13%)
Adrenaline	<50%[†]	5 (4%)	18 (6%)	24 (5%)
Volume expanders	0	1 (0.85%)	12 (4%)	13 (3%)
Any antenatal corticosteroids	2/8 (25%)	52/71 (73%)	181/216 (84%)	235/295 (80%)
Not actively managed and died – n (% livebirths)	181 (95%)	142 (55%)	35 (10%)	358 (45%)
Died prior to nursery admission despite active management	6 (60%)	6 (5%)	14 (5%)	26 (6%)
Admitted to nursery for ongoing active care - n[§]	**<5**	**112**	**296**	**412**
% livebirths	<3%	43%	86%	52%
% actively managed livebirths	40%	95%	95%	94%
ALIVE AT ONE YEAR - n	**0**	**59**	**204**	**263**
% livebirths	0%	23%	59%	33%
% actively managed livebirths	0%	50%	66%	60%

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§ There were 4 infants without resuscitation data recorded who were admitted to the nursery for active care and survived; † Numerator not reported for de-identification purposes; Data are n (% actively managed), unless otherwise specified

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Table 3. Perinatal variables related to a) active management, and b) infant survival in those actively managed

Perinatal variable	**a) Active management in eligible livebirths**			
	Active	Not Active	Odds ratio (95% confidence interval) P-value	
	N=438	N=358	Univariable	Multivariable
Inborn	361§ (82%)	193 (54%)	4.06 (2.94, 5.61) <0.001	2.96 (1.90, 4.62) <0.001
Multiple birth	108 (25%)	121 (34%)	0.64 (0.47, 0.87) 0.005	0.67 (0.44, 1.05) 0.08
Gestational age - weeks; mean (SD)	23.7 (0.5)	22.6 (0.7)	11.9†† (8.7, 16.4) <0.001	12.4†† (8.8, 17.4) <0.001
Male sex	231 (53%)	200 (56%)	0.88 (0.67, 1.17) 0.38	0.78 (0.52, 1.16) 0.22
Birthweight SD score - mean (SD)	0.10§§ (0.82)	-0.07§§ (1.25)	1.18‡‡ (1.02, 1.36) 0.022	1.45‡‡ (1.19, 1.77) <0.001
	b) Infant survival in those actively managed			
	Survived	Died	Odds ratio (95% confidence interval) P-value	
	N=263	N=175	Univariable	Multivariable
Inborn	235 (89%)	126§ (72%)	1.86 (1.14, 3.05) 0.013	1.83 (1.08, 3.08) 0.024
Multiple birth	62 (24%)	46 (26%)	0.87 (0.56, 1.34) 0.52	1.04 (0.65, 1.67) 0.86
Gestational age - weeks; mean (SD)	23.8 (0.4)	23.5 (0.6)	2.38†† (1.62, 3.50) <0.001	2.65†† (1.75, 4.00) <0.001
Male sex	133 (51%)	98 (56%)	0.80 (0.55, 1.18) 0.26	0.80 (0.54, 1.20) 0.28

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Birthweight SD score - mean (SD)	0.18† (0.81)	-0.02† (0.82)	1.36‡‡ (1.06, 1.73) 0.014	1.53‡‡ (1.18, 1.98) 0.001

Data are n (%), unless otherwise specified. §1 missing birthplace; †1 missing data; §§2 missing data; ††per week; ‡‡ per SD.

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Figure 1: Temporal changes in rates of active management and survival to one year

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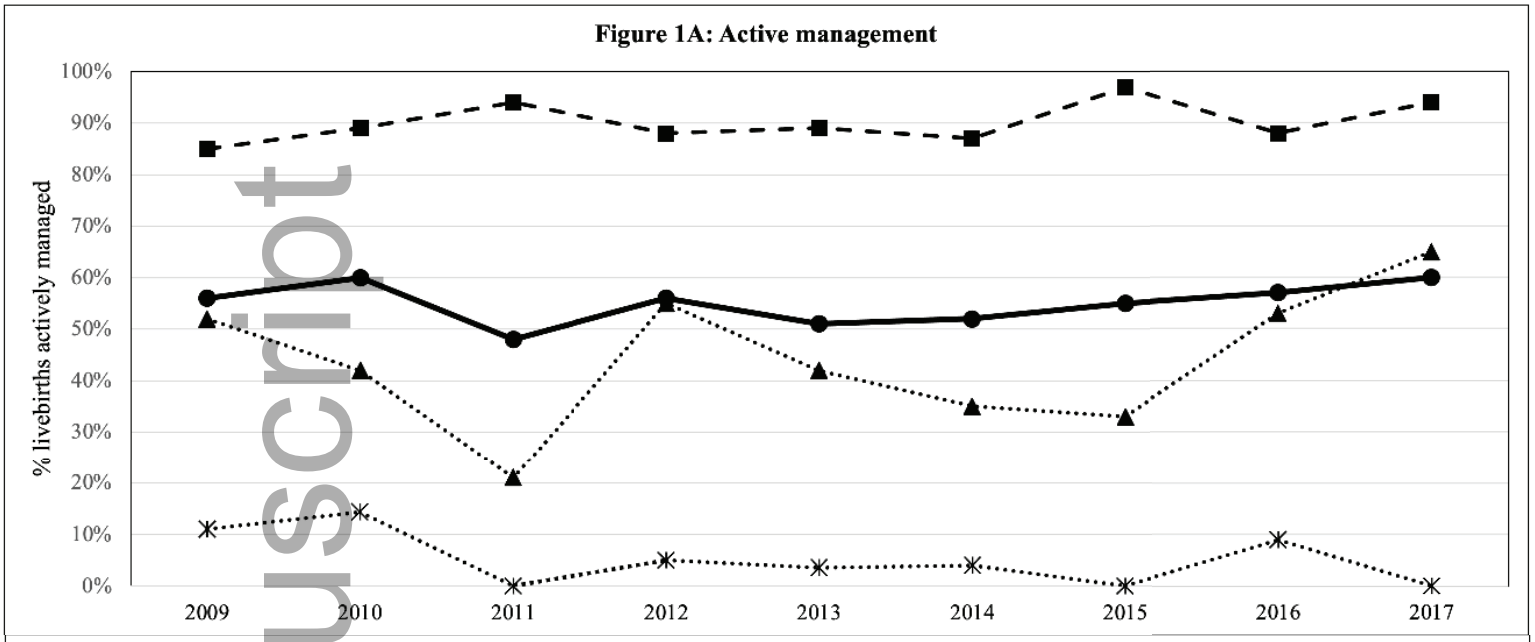
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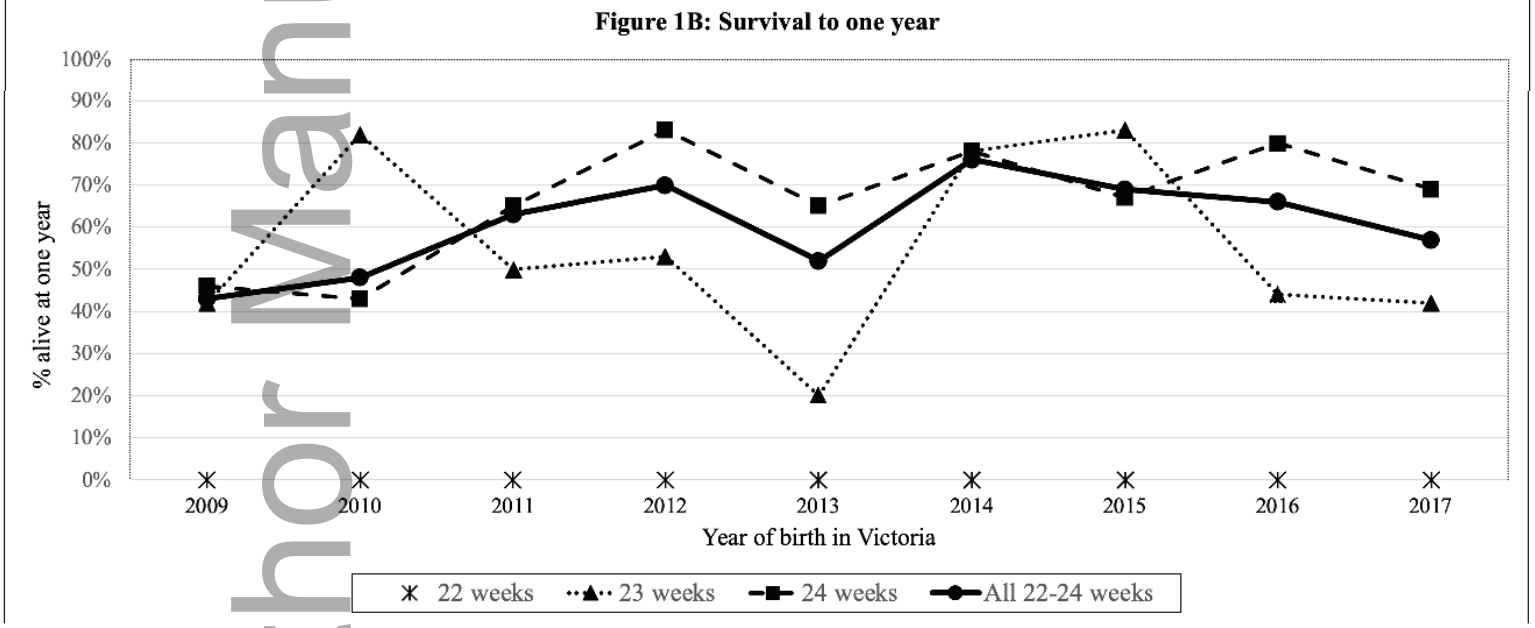
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Figure 1. Temporal changes in rates of active management and survival to one year





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