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RESEARCH ARTICLE

THE IMPACT OF AGE AND FRAILTY IN MULTIPLE MYELOMA PATIENTS' OUTCOME

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ABSTRACT

Frailty score (FS) was developed due to the unfitness of the aging myeloma patients to guide treatment making decisions. However, very few studies validated it in clinical practice. We therefore retrospectively studied 357 symptomatic MM patients, evaluated the impact of FS and age on outcome and compared these variables to other common prognostic factors. FS was estimated following the geriatric assessment formula, while patients were additionally separated into three age groups, up to 60, between 61 and 74 and 75 years old and above. Both FS and age significantly segregated patients with an adverse outcome ($p=0.0007$ and $p<0.00001$ respectively). However, FS was highly predictive of outcome in patients between 61 and 74 years old, while, unexpectedly, common prognostic factors behaved differently in the different age-groups.

Key words: Multiple Myeloma, Frailty Score, prognostic factors

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INTRODUCTION

Multiple myeloma (MM) is a plasma cell dyscrasia, characterized by bone marrow (BM) infiltration by monoclonal, paraprotein-secreting plasma cells. In its symptomatic form, it is a morbid disease with a wide range of clinical manifestations, reflecting end-organ damage and including the CRAB criteria, extend of BM infiltration, serum free light chain ratio above 100 and at least one osteolysis at refined radiology evaluation (Rajkumar, 2014). Therapeutic management has improved in recent years with the emergence of very active biology-driven drugs, thus leading to a significant survival increment (Röllig, 2015). However, over these years the general population survival expectancy has also increased, as well as the rate of myeloma diagnosis in advanced-aged patients, as it is mainly a disease of the elderly (Smith, 2009). Age-related physical, functional, medical or cognitive problems may prevent the administration of some treatments; in consequence, some patients may not be "fit" enough to receive an adequate therapy. Therefore, FS was developed by the International Myeloma Study Group, to assess elderly MM patients' prognosis (Palumbo, 2015a). The score was based on the Geriatric Assessment (GA) formula that involves Renal score, Katz and Akpom's basic activities of daily living scale (BADL) (Katz, 1976), Lawton and Brody's instrumental scale (IADL) (Lawton, 1969) and the Charlson's comorbidity index score (CCIS) (Charlson, 1987). The BADL score is used to assess self-care activities, while the IADL score evaluates functional status. The CCIS is used to estimate the number and severity of comorbidities. Frailty score separates 3 categories: fit patients (frailty score 0), intermediate fit patients (frailty score 1) and finally the frail ones (frailty scores 2, 3, 4 and 5). However, the international myeloma study (Palumbo, 2015a), assessed the impact of FS in patients enrolled in clinical trials and this is a kind of selection. Very few studies validated this score in clinical practice; we therefore aimed to investigate the impact of FS and age, in comparison to other prognostic variables, in a single center MM patients' series of patients treated according to clinical practice.

PATIENTS AND METHODS

Patients

Files from 357 consecutive symptomatic MM patients, diagnosed or treated in our outpatient clinic, from 2000 to 2017, with a median follow-up time of 38 months, were retrospectively reviewed. Prognostic variables comprised in routine diagnostic workout, including complete blood counts, renal function tests, serum calcium, LDH, beta-2 microglobulin (B_2M), protein electrophoresis and immune-

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electrophoresis, quantitative immunoglobulin measurements including free light chains, skeletal imaging (performed by bone survey or low dose computed tomography, according to time periods), BM smears and biopsies, were recorded, as well as Performance Status (PS). Karyotype and FISH studies that were performed only in more recently diagnosed patients were not taken in account; therefore, patients were staged according to Durie-Salmon (D-S) and ISS stages and not with the revised ISS. Patients were further subdivided into fit, intermediate fit and frail according to FS, and also separated into three age groups: less than 60 years old, 61 to74 years old and over 75 years old, to determine in detail, the effect of age beside frailty. Their corresponding stage and MM type are shown in Table 1. According to treatment indications at diagnosis time and institutional practice, 37% of patients received VAD (vincristine-adriamycin-dexamethasone), 26% bortezomib-containing regimen [bortezomib-dexamethasone (VD) or borte zomib-cyclophosphamide-dexamethasone (VCD)], 37% mel phalan-containing regimen [melphalan-prednisone (MP), melphalan-prednisone-thalidomide (MPT),or melphalan-prednisone-bortezomib- (MPV)], and 5% lenalidomide con taining-regimen at first line. Twenty five percent of patients underwent autologous stem cell transplantation (ASCT) after induction. The median number of treatment lines subsequently administered was 4 (1-12).

Methods

FS was retrospectively estimated following the GA formula (Palumbo, 2015a). Informed consent was obtained (see Appendix below). Statistical analysis was performed with SPSS v22.0 software. Common prognostic variables included in the diagnostic work-up, such as hemoglobin, platelet counts, serum creatinine, serum calcium, LDH, b_2M, serum free light chains and their ratio, percentage of bone marrow infiltration by plasma cells, performance status and disease stage were tested in frail patients and in the three age groups. Survival was calculated from diagnosis to last follow-up or death. Survival curves were plotted by Kaplan-Meyer method and assessed by the Log-Rank test. Non-parametric variables were assessed by the Mann-Whitney test or chi-square accordingly. We determined as statistically significant limit p-value <0.05.

Appendix

The FS retrospective assessment presents some difficulties, with regard to IADL and BADL scale. However, as the physician-corresponding/head author followed personally from diagnosis to last follow up the patients, while the rest physician co-authors personally followed during some period of time the patients, they can estimate the patients' abilities in everyday living [eg. They know how patients could dress or undress for physical examination, how they came to the outpatient clinic (alone, with a relative or an accompanying person), if the patients could use a phone by themselves and correctly express their problem, as the physician-authors were directly answering to phone calls made by patients or their relatives every time a patient had a problem. Due to the direct human contact, authors-physicians could sometimes receive flowers from patients' personal gardening or cakes made by themselves etc. All these small things allow valuable retrospective scoring of IADL and BADL scale.

RESULTS

In the total cohort of symptomatic MM patients

Patients' median age was 69 years (range 31-90), while 58% were males. D-S and ISS stages are depicted in Table 1. MM type was IgG in 61%, IgA in 23% and Light Chain MM (LC) in 13% of the population examined, while 5 patients presented IgD, 4 presented biclonal and 2 non-secretory myeloma. Of the above patients 42% were fit (FS 0), 36% were intermediate fit (FS 1) and 22% were frail, while median FS of the whole cohort was 1 (Table 1). Univariate analysis showed that age groups studied presented significant differences in survival ($p<0.00001$) (Figure 1A). With regard to FS, median survival differed significantly in fit, intermediate-fit and frail patients ($p=0.0007$), being 95, 41 and 20 months respectively (Figure 1B). The 3-year 1st line progression free survival (PFS-1) was 34%, 23%, and 5% and the 3-year overall survival (OS) was 77%, 41%, and 30% in fit, intermediate-fit and frail patients respectively (Table 2). The impact of frailty in OS and PFS-1 in our center in comparison to the IMWG cohort (Palumbo, 2015a), and Engelhardt et al study (Engelhardt, 2017) is also shown (Table 3).

Other classical prognostic variables that significantly correlated with OS were Durie-Salmon stage ($p<0.00001$), ISS stage ($p=0.0004$), abnormal LDH ($p=0.001$), abnormal calcium ($p=0.002$), BM infiltration equal or over 60% ($p=0.0009$), serum creatinine levels equal or over 2.5 mg/dL ($p=0.0008$), platelet number (PLT) below 100,000/μL ($p<0.0001$), Hemoglobin (Hb) levels equal or under 10 gr/dL ($p=0.0003$), and high Free Light Chain Ratio (FLCR) (equal or above median values for monoclonal lambda and kappa FLC: ≤ 0,042 and ≥ 33,29) ($p=0.002$). PS was also significantly correlated to OS ($p=0.0004$) (Table 4).

Frail MM patients

The number of frail patients (FS≥2) of our study was 79 of whom 29% had frailty score 2, while 60%, 9% and 2% had scores 3, 4, and 5 respectively. Their median age was 76 years (range 41-90), and their median OS 20 months with only 9% remaining alive. Males accounted for 51% of the population. The majority was in advanced D-S and ISS stage (67% and 68% respectively in stage III). Their MM type was proportionate to that of the whole cohort (Table 1). Among prognostic variables examined, only abnormal LDH ($p<0.0001$) and abnormal calcium ($p=0.002$) were significantly correlated to OS. PS tended to correlate to OS, but not significantly ($p=0.116$) (Table 4). Regarding treatment of frail patients, the majority of them (54%) with a median survival of 24 months, received at first line a melphalan-prednisone-containing regimen, either MP alone or MPT or MPV, 30% received other bortezomib-containing ones, while 10% received lenalidomide-dexamethazone and the rest (6%) received other various regimens. Thirty-two percent of frail patients succumbed during first line treatment while the other patients received further lines including new agents in next lines (mostly lenalidomide).

Subgroup of MM patients ≤60 years

Young symptomatic MM patients included in the study were 85, with a median age of 53 years (range 31-60), while 58% were males. Fifteen percent, 24% and 61% were classified as D-S stage I, II and III respectively, while 38%, 22% and 40% were ISS stage I, II and III respectively. Their MM type was IgG in 60%, IgA in 22% and Light Chain MM (LC) in 15%, while 1 patient presented IgD and 1 non-secretory myeloma About one third of them were fit (27%), one third were intermediate fit (38%) and one third were found to be frail (35%). Their median OS was 86 months with 34% being alive (Table 1).

Table 1: Patients' Characteristics

	MM ALL	Frail	≤60	61-74	≥75
Number	357	79	85	168	104
AGE	69 (31-90)	76 (41-90)	53(31-60)	68.5 (61-74)	79 (75-90)
SEX(M-F)	207 (58%)-150 (42%)	40 (51%) - 39 (49%)	49 (58%) - 36 (42%)	101 (60%) -67 (40%)	57 (55%) - 47 (45%)
Staging:					
D-S I	57 (16%)	6 (8%)	13 (15%)	27 (16%)	17 (16%)
D-S II	107 (30%)	20 (25%)	20 (24%)	54 (32%)	33 (32%)
D-S III	193 (54%)	53 (67%)	52 (61%)	87 (52%)	54 (52%)
ISS I	82 (23%)	6 (8%)	32 (38%)	40 (24%)	9 (8.65%)
ISS II	107 (30%)	19 (24%)	19 (22%)	54 (32%)	35 (33.65%)
ISS III	168 (47%)	54 (68%)	34 (40%)	74 (44%)	60 (57.7%)
MM type:					
IgG	218 (61%)	49 (62%)	51 (60%)	99 (59%)	71 (68%)
IgA	82 (23%)	14 (18%)	19 (22.35%)	40 (24%)	21 (20%)
LC	46 (13%)	12 (15%)	13 (15.3%)	22 (13%)	10 (10%)
Other types*	11 (3%)	4 (5%)	2 (2.35%)	7 (4%)	2 (2%)
			IMWG frailty score		
0 (fit)	151 (42%)		2 (27%)	32 (19%)	10 (9.6%)
1 (intermediate fit)	127 (36%)		32 (38%)	71 (42%)	33 (31.7%)
≥2 (frail)	79 (22%)		30 (35%)	65 (39%)	61 (58.7%)

D-S: Durie-Salmon, *Other types include IgD, biclonal and non-secretory myeloma

Table 2. Patients' characteristics in comparison to previous publications on frailty score

	Our Study	Palumbo et al., (Palumbo, 2015a)	Engelhardt et al., (Engelhardt, 2016)	Zhong et al., (Zhong, 2017)
Number	357	869	125	628
AGE	69	74	63	58
CCIS	2	0	2	0
IMWG frailty score				
0 (fit)	45%	39%	18%	20%
1 (intermediate-fit)	33%	31%	34%	16%
≥2 (frail)	22%	30%	48%	64%
3y-OS in fit patients	77%	84%	91%	63%
3y-OS in intermediate fit patients	41%	76%	77%	63%
3y-OS in frail patients	30%	57%	47%	49%
3y PFS-1 in fit patients	34%	48%	43%	NA
3y PFS-1 in intermediate-fit patients	23%	41%	25%	NA
3y PFS-1 in frail patients	5%	33%	22%	NA

OS: Overall Survival, **PFS-1:** 1st treatment line Progression Free Survival, **NA:** Not Available

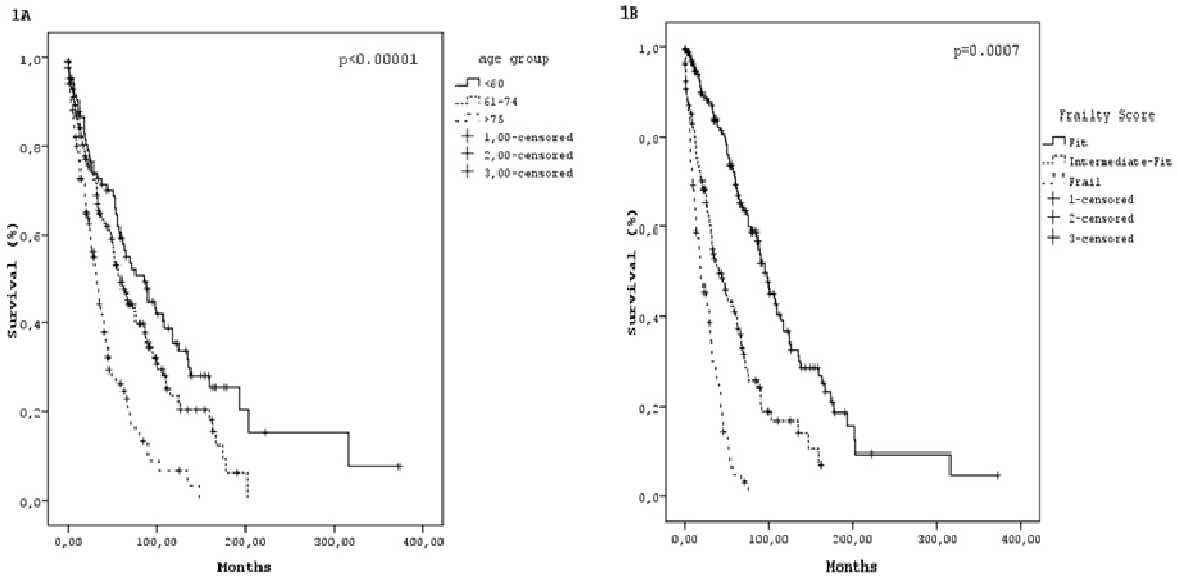

Figure 1: Survival curves in different age groups (1A) and frailty score groups (1B).

Table 3. The impact of frailty on OS and PFS-1 in our study, in comparison to previous publications in FS

IMWG score	Patient's Status	Our Study				Palumbo *et al.,* (Palumbo, 2015a)				Engelhardt *et al.,* (2016)				Zhong *et al.,* (2017)			
		PFS-1 HR (95% CI)	p	OS HR (95% CI)	p	PFS-1 HR (95% CI)	p	OS HR (95% CI)	p	PFS-1 HR (95% CI)	p	OS HR (95% CI)	p	PFS-1 HR (95% CI)	p	OS HR (95% CI)	p
0	Fit	1		1		1		1		1		1		NA		1	
1	Intermediate fit	0.68 (0.51-0.92)	0.013	0.62 (0.45-0.85)	0.003	1.18 (0.91-1.53)	0.211	1.61 (1.02-2.56)	0.042	1.19 (0.56-2.55)	0.648	1.77 (0.36-8.75)	0.487	NA	NA	0.97 (0.39-2.4)	0.939
≥2	frail	0.64 (0.48-0.85)	0.002	0.37 (0.27-0.51)	0.0001	1.68 (1.31-2.15)	0.001	3.57 (2.37-5.39)	0.001	1.90 (0.94-3.86)	0.075	5.80 (1.35-24.96)	0.018	NA	NA	1.61 (0.83-3.12)	0.159

PFS-1: 1st treatment line Progression Free Survival, HR: Hazard Ratio, **OS:** Overall Survival, **NA:** Not Available

Table 4: Prognostic significance of disease variables on OS in each patients' group

	MM ALL	Frail	≤60	61-74	≥75
Frailty score	p=0.0007	NS	NS	p<0.00001	NS
D-S	p<0.00001	NS	NS	p<0.00001	P<0.00001
ISS	p=0.0004	NS	p=0.006	p=0.001	p=0.017
Incr LDH	p=0.001	p<0.0001	NS	p=0.023	p=0.011
Incr Ca	p=0.002	p=0.002	p=0.003	p=0.001	p=0.12
BM≥60%	p=0.0009	NS	p=0.022	p=0.0001	NS
cr≥2.5	p=0.0008	NS	p=0.035	p=0.008	NS
PLTs<100 x 10^9/L	p<0.0001	NS	NS	p=0.004	NS
Hb ≤10g/L	p=0.0003	NS	p=0.022	p=0.001	NS
FLCR-high*	p=0.002	NS	p=0.002	p=0.028	p=0.003
B_2M≥5.5mg/dL	p<0.00001	NS	p<0.00001	p<0.00001	p=0.003
PS	p=0.0004	0.116	p=0.0001	p=0.0006	p=0.032

Incr=Increased, Ca=Calcium, FLCR=Free Light Chain Ratio, BM= Bone Marrow, Cr= creatinine, PLTs=Platelets, Hb=Haemoglobulin, PS= Performance Status

In that age group, FS failed to correlate to OS, while PS correlated significantly (p=0.0001). Prognostic variables with statistical significance were ISS (p=0.006), abnormal calcium (p=0.003), serum creatinine levels equal or over 2.5 mg/dL (p=0.035), Hb levels ≤ 10 gr/dL (p=0.022), BM infiltration equal or over 60% (p=0.022), high FLCR (p=0.002) as well as B_2M≥ 5.5mg/dL (p<0.00001) that is indeed included in ISS (Table 4).

Subgroup of MM patients 61-74 years: This subgroup was the larger one including 168 patients with a median age of 68.5 years (range 61-74), and 60% of them being males. Their D-S and ISS stages as well as their MM type were proportionate to that of the whole cohort (Table 1). Nineteen percent of them were fit, 42% were intermediate-fit, while 39% were frail (with 15%, 22% and 2% having scores 2, 3 and 4 respectively). Patients' median OS in this group was 60 months with 36% being alive. In this age group, all classical prognostic factors studied, strongly predicted outcome as shown by univariate analysis; FS prognostic power was optimal (p<0.00001), as did PS (p=0.0006) (Table 4).

Subgroup of MM patients (≥75 years)

This subgroup of elderly symptomatic MM patients included 104 patients, with a median age of 79 years (range 75-90), while 55% were males. Sixteen percent, 32% and 52% were classified as D-S stage I, II and III respectively, while 9%, 34% and 57% were ISS stage I, II and III respectively. Their MM type was IgG in 68%, IgA in 20% and Light Chain MM (LC) in 10%, while 1 patient presented IgD and 1 biclonal myeloma (Table 1). A small proportion of them were fit (9%), one third were intermediate-fit (32%), while the majority were frail (59%) (With score 2 in 16%, 3 in 32%, 4 in 9% and 5 in 2% of the above population). Their median OS was 31 months with 25.5% being alive. Indeed, as the majority were frail, FS failed to correlate to OS (p=0.516). Significant determinants of outcome were only stage, abnormal LDH, high FLCR and PS (Table 4).

DISCUSSION

MM is a common hematologic malignancy, with a higher incidence in elderly people (Palumbo, 2011a; Lenhoff, 2006). With population longevity increment, an augmentation is expected in the number of elderly myeloma patients to be diagnosed in the forthcoming years (Rosenberg, 2015). While the introduction of immunomodulatory agents and proteasome inhibitors over the past decade has improved survival mostly in younger patients, in older ones this has happened to a less extend, (Pozzi, 2013; Kumar, 2013; Kumar, 2008), possibly because of a higher frequency of treatment discontinuation, non hematological adverse events and inability to receive effective therapy (Palumbo, 2015a; Palumbo, 2011b, Palumbo, 2015b; Mellqvist, 2015; Kleber, 2013; Kleber, 2012) or to comply with it. Advanced age by itself, is proven to be one of the strongest prognostic factors and survival decreases steadily with each decade of age (Ludwig, 2010). With increasing age however, there are no "easy" borderlines to be set as some patients retain their fitness while others become frail. Thus, until recently all elderly myeloma patients were categorized empirically by clinical judgment as their fitness was concerned. Frailty is an age associated biological syndrome, leading to decreased biological reserves and to an increased risk for individuals under stress rendering them vulnerable (Clegg, 2013; Rodrvguez-Mapas, 2013). It is very common in people older than 65 years old, associated with poor outcomes (Fried, 2001). To avoid undertreating a priori older yet fit patients (Kleber, 2013; Engelhardt, 2014; Offidani, 2012), Palumbo and the International Myeloma Working Group (IMWG) established FS that combined age, functional status and comorbidities to predict survival and therapeutic toxicity, as a useful tool for treatment schedule (Palumbo, 2015a).

In a pooled analysis of 869 patients with newly diagnosed MM from three clinical trials, the investigators revealed 3-year OS of 84% in the fit, 76% in the intermediate-fit and 57% in the frail category. Grade 3-4 nonhematological toxicity was 22%, 26%, and 34% in the fit, intermediate-fit and frail group, respectively. Lastly, treatment discontinuation increased from 16% in the fit to 21% in the intermediate-fit and to 31% in the frail group. Recently Engelhardt and colleagues validated the IMWG score in a study of 125 newly diagnosed myeloma patients, revealing 3-year OS for fit, intermediate-fit and frail patients of 91%, 77% and 47% respectively (Engelhardt, 2016).

However, since the IMWG predictive model was developed in clinical trial patients, selected according to strict inclusion criteria, external validation is required in routine clinical practice. Even in Engelhardt's et al study that was been conducted to validate this score in clinical practice, 40% of patients were enrolled in clinical trials at first line (Engelhardt, 2016). A recent multicenter retrospective study contacted in 628 Chinese patients revealed a 3-year OS of 63% in the fit and intermediate fit patients and 49% in the frail ones, while treatment discontinuation was reported in 20% in fit, 22% in intermediate-fit, and 35% in frail patients (Zhong, 2017). We aimed to investigate the impact of frailty score and age, in comparison to other prognostic variables, still in a single center series of myeloma patients treated in real life clinical practice. Indeed, different therapies were administered, as for the two previous studies, but always according to EMA (European Medical Agency) indications and current practice of the period patients were diagnosed.

In our study, we had a slightly lower percentage of frail patients (22%) than in the two preceding studies (Table 2). FS prognostic potential was found significant with regard to OS but also more potent than the other studies with regard to PFS-1 (Table 3), possibly because our patients were treated with less active drugs. Frailty score strongly correlated to OS, mostly in the 61-74 years old subgroup ($p<0.0001$), failing to predict outcome in the young and very old patient subgroups. Thus, it seems that young patients (<60 years old) are generally in a better physical condition, even when being frail, and can overcome the adverse impact of frailty. In order to determine the effect of age besides frailty, patients were separated into three age groups: less than 60 years old, 61-74 years old and over 75 years old and thus we confirmed that age is indeed a strong prognostic factor. Another notable finding of our study is that classical prognostic factors of survival in symptomatic MM patients had not the same value in frail patients and in the different age groups. Likewise, in frail patients, only increased serum LDH and calcium were prognostic. Abnormal LDH and increased calcium are two well-known adverse prognostic factors, recently re-validated (Palumbo, 2015b; Zagouri, 2017). Increased calcium was or tented to be predictive of adverse outcome in all patients' groups while LDH in all but the young ones that were more alike to receive new agents' combination and ASCT; the reason could be that some novel treatments may overcome the adverse impact of adverse prognostic factors (Kyrtsonis, 2011).

In frail and aged patients, renal function and hemoglobin were not statistically significant predictors of survival, probably because elderly women constituted half of the population studied and, in advance age women's renal function is normally impaired to some extend causing chronic renal failure that in turn lead to a degree of anemia; the phenomenon is indeed more marked in frail patients for whom the most frequent co-morbidities are diabetes and hypertension, both further impairing renal function and in turn increasing B_2M thus rendering ISS stage and indeed B_2M not prognostic. In conclusion, as MM is a typical disease of the elderly, patients' "vulnerability" ought to be taken in account. Undoubtedly, in patients with MM, treatment should not be withheld solely on the basis of age. Whether FS is the best or not remains to be proven, as an increasing number of investigations are proposing slightly different scores (Rodríguez-Otero, 2018; Gregersen, 2017; Huisingh, 2017).

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